JANUARY 1955

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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ASTHMA, EMPHYSEMA AND CHRONIC PULMONARY INFECTIONS

Transcription of a Panel Meeting

DICKINSON W. RICHARDS
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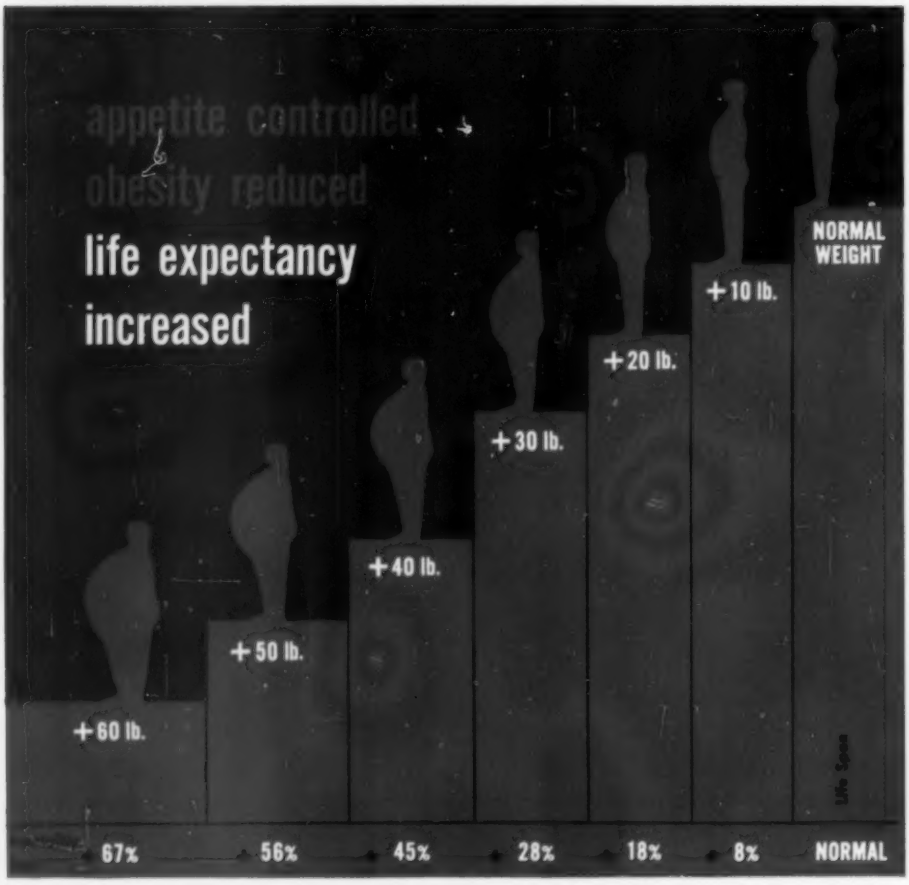

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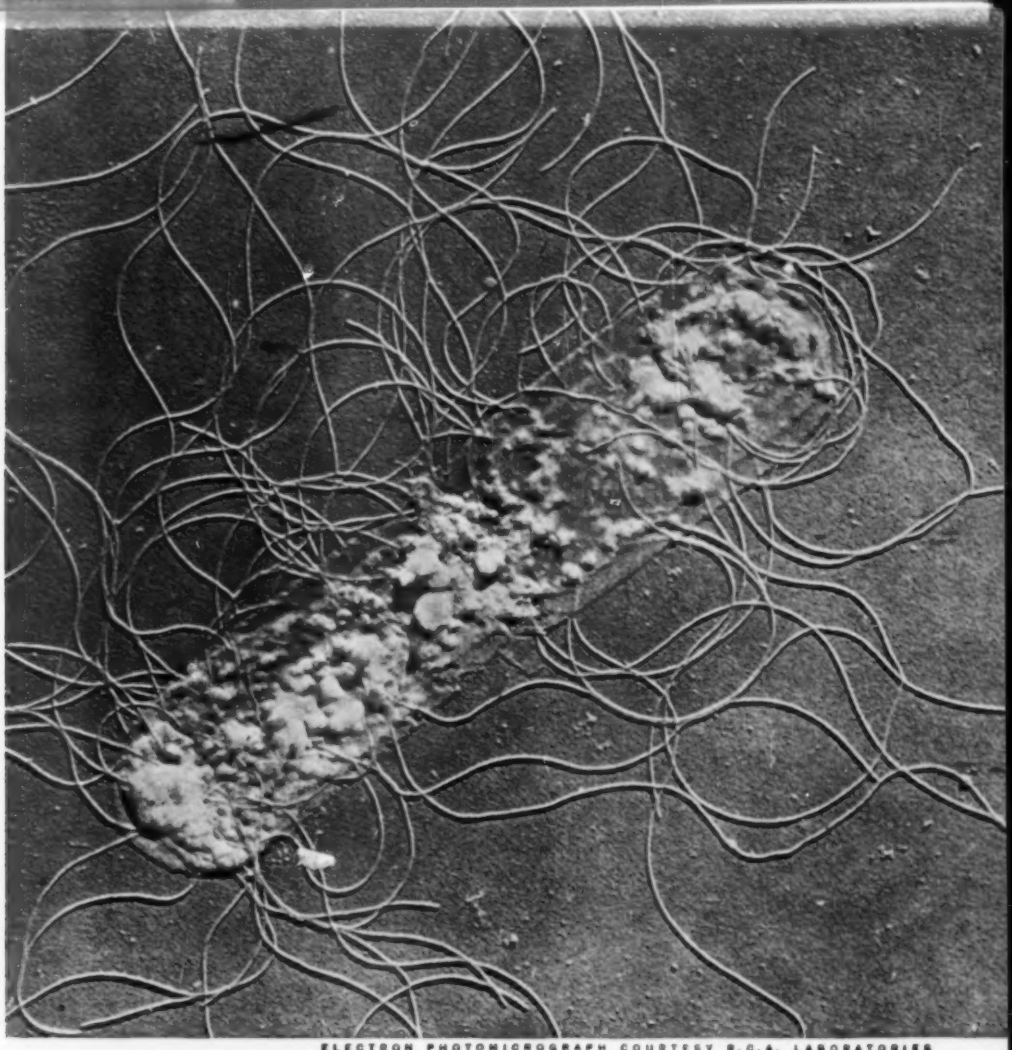

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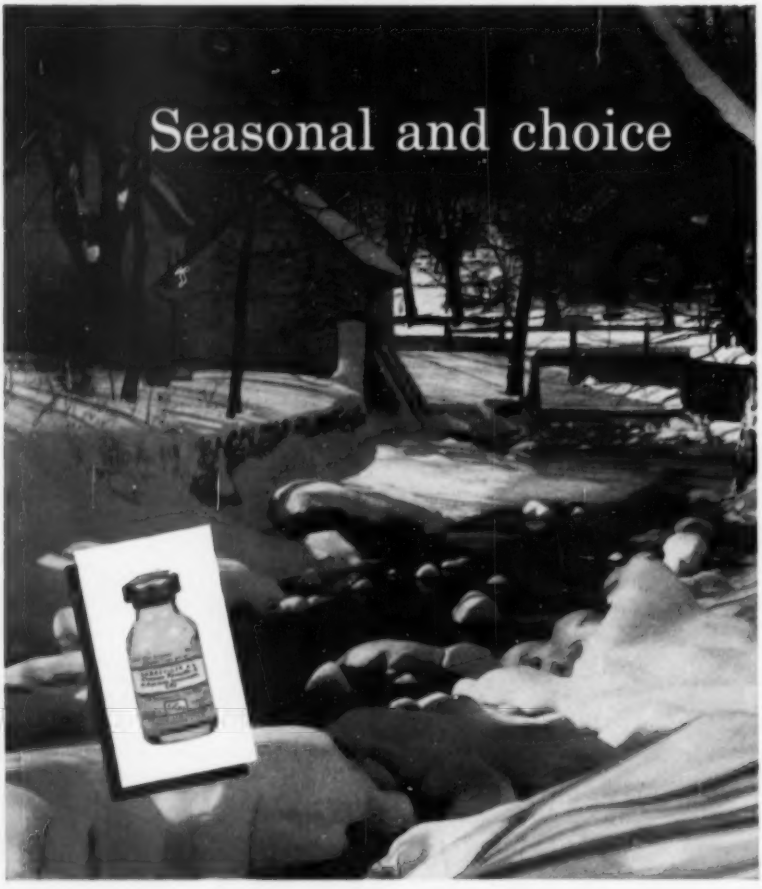

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
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VOL. 31, NO. 1 JANUARY 1955

OPENING ADDRESS*

Twenty-Seventh Annual Graduate Fortnight

ALEXANDER T. MARTIN

President, The New York Academy of Medicine

IN OPENING this Twenty-Seventh Annual Graduate Fortnight, I want, at the outset, to bear witness to the long term planning necessary to arrange this program and to pay tribute to the effort and time expended by so many of our doctors—Fellows and non-Fellows alike. Over 140 practitioners, teachers and investigators have taken part in and are contributing to this Fortnight of postgraduate education, and it is significant that it has become one of the most important medical educational events in this country. Special acknowledgment and commendation are due the Subcommittee on the Graduate Fortnight under the chairmanship of Dr. David Seegal, who presides this evening.

Six morning panel meetings have been arranged by the special committee on panels, with Dr. Eichna as chairman. These panel sessions give to the practicing physician an opportunity to participate in the discussions of the panel group, and in the past have proved most valuable and popular.

The Scientific Exhibit has always been an important educational feature of the Fortnight. Our thanks are due to Dr. Angrist and Dr.

* Presented October 18, 1954, at The New York Academy of Medicine.

Higinbotham for their efforts in organizing and arranging this year's excellent exhibit. This has been a large task for all those concerned.

The special committee on Hospital Clinics, with Dr. Rousselot as chairman, has arranged afternoon clinics in eleven hospitals. And so the practicing physician and the student should have his or her time well and profitably filled for these two weeks.

The subject chosen, "Infections and Their Management," is a timely one, and from this platform there will be presented the considered and distilled wisdom and experience of a score of outstanding authorities in their field. We are grateful to these participants for their contributions.

Tonight two honorary lectureships will be given, the Ludwig Kast and the Harlow Brooks lectures. The Wesley M. Carpenter lecture will be presented tomorrow night. The Academy thus honors three of its distinguished former Fellows.

Our Library has contributed to this Fortnight program by preparing important and interesting exhibits on the subject of infection and I would urge everyone to view these exhibits. They are a small sample of the great treasures (nearly 300,000 volumes) which the shelves of our Library hold and which play such a large and essential part in medical education. Our Library treasures a sample of the original Penicillium notatum. This was presented by Sir Alexander Fleming to Miss Ruth Draper, who in turn presented it to the Academy. The occasion was a particularly happy one, as Sir Alexander was present in person at the presentation. Unfortunately, the penicillium mold, beautifully mounted, is off on tour, and is now in Chicago on exhibit. We regret that we cannot show you this during the present Fortnight.

Sustained activity in the field of continuing medical education is one of the chief functions of the Academy of Medicine and our Fortnight is arranged and sponsored by the Academy's Committee on Medical Education, of which Dr. Franklin M. Hanger is chairman.

Special recognition and appreciation of services is made to Dr. Robert L. Craig, Executive Secretary of the Committee on Medical Education, and his able staff, for the all-important task of making this Fortnight a reality.

It is my hope that all of you will benefit from this feast of knowledge and will return to your communities, wherever they may be, the better equipped to practice good medicine and thus raise the quality of medical care. Given this assurance, the Fortnight will have served its purpose and the Academy will have performed one of its chief functions, that of medical education.

BIOCHEMICAL DETERMINANTS OF INFECTION*

The Ludwig Kast Lecture†

RENE J. DUBOS

Member, Rockefeller Institute for Medical Research

GEORGE BERNARD SHAW affected great scorn for medical science and particularly for the germ theory of disease. "The characteristic microbe of a disease might be a symptom instead of a cause" he asserted in the preface of his play "The Doctor's Dilemma." Few are those who take seriously Shaw's views regarding science. Yet, I wonder at times whether his aphorism was not a prophetic statement—even though somewhat fanciful in wording—of a problem which has come to occupy a prominent place in the field of infectious diseases.

Consider for example the perplexing riddles posed by the existence of silent or latent infections. Pathogens of all kinds—protozoa, fungi, bacteria, rickettsia, viruses can persist in an active form in the tissues of a susceptible host, without causing detectable lesions or symptoms. These latent infections can remain unnoticed for the life time of the infected individual, the host and the parasite ignoring or at least tolerating each other under normal conditions. Let the proper kind of physiological disturbance occur in the host, however, and the equilibrium is upset. At times, probably, the parasite is eliminated altogether. More often, it starts proliferating in an uncontrolled manner, the latent infection evolving into overt disease. Shaw was wrong of course in stating that the microbe was the consequence of the disease. But there was truth in his aphorism since in many cases something has first to happen to the patient before the microbe can multiply extensively enough to cause symptoms and lesions.

The problem of latent infections acquires large practical importance from the fact that many infectious diseases in our communities are caused

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, October 18, 1954.

† In honor of Dr. Ludwig Kast who first suggested the Graduate Fortnight.

by microorganisms which are widely distributed among normal, healthy members of the population. There is little doubt that a great part of the increase in the prevalence of infectious diseases observed under certain disturbed social conditions is due to the fact that widespread physiological misery tends to activate latent endemic infections. A group of Danish physicians who were interned in German concentration camps during the last war have made observations which are very instructive in this respect.[1]

Among infectious diseases, it was not the exotic, unusual epidemics, such as typhus, cholera, or even bacillary dysentery, which proved the most troublesome in their experience, but rather ordinary skin ailments, colds, bronchopneumonias, staphylococcus infections, pulmonary tuberculosis – in other words, the type of disease, benign or severe, caused by microorganisms endemic in the normal European communities. Increase in contact infections could hardly account for the aggravation of these endemic diseases. Far more important certainly was the loss of natural resistance caused by malnutrition and other forms of physiological misery. It was remarkable indeed that most of the Danish internees overcame their microbial maladies shortly after their return to a normal environment and often without the help of specific therapy. Rapid recovery was the rule even in the case of tuberculosis, though no antimicrobial agent was then available for its treatment. The happenings in the concentration camps are directly relevant to our present topic because they can be regarded as the magnified manifestation of a state of affairs observed daily in medical practice.

During the past two decades, many types of substances, procedures, or accidents have been found capable of bringing about conditions under which latent microorganisms can manifest their potential pathogenicity and cause overt disease in man, animals, and plants. We shall briefly mention a few examples, selected not on the ground of their practical importance, but merely to illustrate two points: on the one hand, the variety of agents which are capable of *provoking* – as the expression goes – latent microorganisms into activity; on the other hand, the range of pathological states which can thus be evoked out of symptomless infections.

Intranasal injection of sterile broth or unheated serum into the nasal cavity of normal healthy mice brings about in a large percentage of these animals the development of pulmonary lesions caused by a variety of filtrable viruses latent in their lungs.[2-4]

In certain strains of mice the stresses and hormonal activity associated with reproduction and lactation determine the occurrence of mammary carcinoma in a large percentage of animals infected with the Bittner virus, whereas this infection remains symptomless in males or in virgin females.[8]

Mice or rats treated with large amounts of cortisone, or subjected to intense radiation, or placed on certain deficient diets, develop fatal pseudotuberculosis caused by Corynebacterium pseudotuberculosis murium.[9-10]

Cortisone, as is well known, can enhance many various types of latent infectious processes (reviewed in references 11 and 12), causing for example the activation of latent trypanosomiasis in a very large percentage of normal monkeys.[13]

Physical trauma brings about in dogs the proliferation of latent clostridia which convert traumatic shock into irreversible shock through the action of their toxins.[14]

In man the fever blisters which are caused by the herpes simplex virus and follow up many types of febrile episodes,[15] the moniliasis and aspergillosis associated with debilitating diseases or following treatment with antibacterial drugs,[16, 17] the reawakening of old tuberculous lesions by any form of physiological misery, the activation of toxoplasmosis by childbirth,[18] are but a few examples of latent infections which remain unnoticed under normal conditions but are provoked into activity by non-specific disturbances.

* * * *

While there is no knowledge of the precise mechanisms by which latent infections can be converted into active disease, at least two of the possibilities that first come to mind appear to be ruled out. The activation of the infectious process does not seem to result from the loss by the host of specific protective immunity—humoral or cellular; thus the herpetic individual who develops fever blisters possesses in his serum neutralizing antibodies against the herpes virus. Nor does the provoking agent exert its effect through increasing the virulence of the potential pathogen, as shown by the following example. Normal guinea pigs inoculated with BCG do not develop progressive infection although living bacilli persist for long periods of time in their tissues. If however the animals are made to inhale silica dust, BCG tuberculosis develops with production of cavities at the site of the silicotic reaction and death often ensues. Yet, the bacilli recovered from the lesions are found to be just as attenuated in virulence as those originally injected into the guinea pig. It is apparent therefore that silicosis acts as a provoking agent of the tuberculous process, not by increasing the virulence of the BCG bacilli, but by paralyzing the resistance which the tissues of the guinea pig normally possess against these microorganisms.[19]

Whatever the nature of the reactions through which provoking agents decrease the resistance of the host, either systemically or locally, one of their effects in all likelihood is to alter the physicochemical environment in the tissues involved. This in turn is bound to influence the severity of the disease since the multiplication and viability of microorganisms, as well as their toxic properties, are conditioned by the composition of the environment. In order to understand the role played in the evolution of the infectious process by changes in the physicochemical characteristics of the tissues, it would be necessary to have a precise knowledge of the conditions under which microorganisms find themselves in vivo. Unfortunately, very little is known in this regard.

At first sight, it would appear that the in vivo environment is merely the physiological *milieu intérieur* determined by the homeostatic mechanisms of the body. In reality, however, the particular environment in which the infectious process follows its course is far different from that termed "physiological." Most microorganisms are taken up by phagocytic cells as soon as they are introduced into the body, the first phase of infection being thus intracellular. Only in a later phase does necrosis cause them to be released into the abnormal extracellular environment of the lesions. The problem is hardly simpler for extracellular infections. It is true that the microorganisms find at first in blood and lymph conditions corresponding to those of the physiological *milieu intérieur*. But the host soon responds to the presence of parasites by the complex and variable reactions referred to under the generic name of inflammation. There is no doubt that the inflammatory zone differs biochemically from the normal tissues and body fluids. Although little is known of the physicochemical conditions prevailing both intracellularly within phagocytic cells and extracellularly within the lesions, a few facts appear worth recording.

It has been demonstrated that leukocytes can produce large amounts of lactic acid and it is probable that their intracellular pH following phagocytosis is rather low (reviewed in reference 20). Similarly, it is certain that the pH of inflammatory exudates is commonly very acidic (values as low as pH 5.3 have been reported) in part at least as a result of the local accumulation of lactic acid produced by inflammatory cells and perhaps also by fixed tissue cells[21, 22] (reviewed in reference 20).

On the other hand it is very likely that the oxygen supply to many lesions or parts of lesions is greatly reduced by the crowding of migra-

tory cells, vascular thrombosis, and other interference with blood flow. These same factors contribute also to increasing locally the CO_2 tension.

Finally, all lesions being the sites of necrotic changes, a great variety of substances resulting from the breakdown of tissue cells accumulate in them; many of these substances are known to affect profoundly the fate and behavior of pathogenic agents (reviewed in reference 20).

Thus it is clear that microorganisms exist in vivo in an environment which is highly complex and abnormal. In final analysis, the physicochemical characteristics of this environment are determined by the biochemical activities of tissue cells; these activities are not constant but instead vary with the metabolic state of the individual. Since the range of metabolic variations is certainly very large, and knowledge concerning this subject very scant, there is much artificiality in the selection of any particular item for emphasis. Granted the arbitrary character of the choice made in the following discussion, it seems worth pointing out nevertheless that certain physiological disturbances are probably reflected in the metabolism of inflammatory cells, modifying their phagocytic activity, their ability to produce lactic acid, even resulting in the abnormal production of other organic acids. As examples, one need only mention the ketosis of uncontrolled diabetes or starvation, or the low glycolytic activity exhibited by the leukocytes of the diabetic individual,[23] or the altered metabolism of tissue cells to which cortisone has been added in vitro.[24]

Before discussing the possible relevance of metabolic disturbances to the phenomena of infection, it may be useful to mention that the various organic acids produced by tissue metabolism differ profoundly in their ability to support bacterial growth. Experiments in vitro with tubercle bacilli, staphylococci and Friedländer bacilli have revealed that lactic acid in concentrations of the order of 0.01 M can inhibit the growth of these organisms and moreover can bring about their death if the environment is anaerobic. The bacteriostatic and bactericidal effects are the more pronounced, the more acid the reaction. Thus, lactic acid possesses antibacterial activity precisely under the conditions which normally exist in inflammatory areas. In contrast, most keto acids and polycarboxylic acids favor bacterial growth under the very same conditions, and indeed can protect microorganisms against the toxic action of lactic acid.[20, 25]

Needless to say, it is not easy to prove that these in vitro findings

have any bearing on the events of infection in vivo. It seems reasonable to believe nevertheless that general metabolic disturbances are reflected in the biochemical activity of phagocytic and inflammatory cells, and must thereby affect the course of infectious processes through their action on the fate and activities of microorganisms in the tissues. Suggestive evidence of this relationship is found in the great susceptibility to infection associated with uncontrolled diabetes and with acute starvation. It is of interest in this respect that the resistance of starved and diabetic individuals becomes normal again when these patients are returned to a satisfactory nutritional state, or when their diabetes is brought under control by adequate insulin therapy. In other words, it appears that susceptibility to infection in these cases is the expression of a reversible disturbance, probably biochemical in nature.

Knowledge is not sufficient to permit a systematic analysis of the mechanisms through which metabolic disorders of the host can affect susceptibility to infectious diseases. Indeed, it is only during recent years that attempts—still very primitive—have been made to study this problem experimentally. We shall outline briefly some of the results obtained in trying to modify the course and outcome of infection by treatments designed to alter the metabolism of the infected animals.

* * * *

There is a general belief that malnutrition plays an important part in increasing susceptibility to infectious diseases. Surprisingly enough, however, it is not easy to find either clinical or experimental evidence to support this view. As has been aptly said the relationship is "made conspicuous more by reiteration than by demonstration."[26] In fact, there is on record well documented evidence that experimental animals fed diets deficient in some essential growth factor can be more resistant to infection than animals fed complete diets (reviewed in references 26 and 27). Instances to the case are thiamine deficiency in experimental poliomyelitis of mice and PABA deficiency in malaria of rats and monkeys.[28] The complexities of the relation between general nutritional state and susceptibility to infection have been critically analyzed in a number of recent reviews.[26, 27, 29-32]

Out of the mass of often conflicting data bearing on the relation between nutritional state and susceptibility, one general conclusion at least is beginning to emerge. The nutritional factors which have been

shown to be essential for growth and reproduction rarely if ever play a decisive and specific role in resistance to infection. True enough, aggravation of disease has been observed in infected animals fed diets deficient in one or the other vitamin. However, the results have been clear cut only in cases where the vitamin deficiency was so profound as to impair greatly the overall physiological well being of the animals.

Convincing evidence that the factors important for growth may differ from those which play a part in resistance to infection has come from the study of mouse salmonellosis. Resistance to this disease can be predictably increased by adding to the diet small amounts of a fraction from germinating wheat or barley (unidentified chemically) which does not modify the growth rate of uninfected animals.[33] Furthermore, certain types of diets which are very unsatisfactory from the point of view of their ability to support growth and reproduction in uninfected mice, do not in any way decrease their resistance to tuberculosis and may even be superior in this regard to diets that appear optimal according to ordinary nutritional criteria.[25, 30, 34] It is worth noting that despite common belief, the protein content of the diet does not have a direct bearing on resistance to infectious disease, at least as found in experimental infection with salmonella and tubercle bacilli.[27, 30, 33, 35, 36]

Recent findings indicate that in many cases at least the nutritional regimen alters resistance to infection indirectly through its effect on the metabolism of the infected animals. Mice fed ad lib diets considered optimal according to all nutritional criteria proved extremely susceptible to tubercle bacilli, staphylococci and Friedländer bacilli if deprived of food for periods of thirty hours (Tables I and II).[37, 38] Resistance to infection returned to normal within a few hours after food had again been provided to the animals.[38] Mice thus rendered susceptible by fasting lost little weight and regained it rapidly. In contrast, the course of infection was not aggravated in mice which were prevented from gaining weight by being maintained in a state of chronic undernutrition by limiting to a low, but constant level, either their total food intake, or the protein content of their diet[36, 37] (reviewed in reference 27).

It is difficult to attribute the infection-enhancing effect of acute but short periods of fasting to deficiencies in essential nutritional factors. It seems more likely that this effect is due instead to the transient production or accumulation in the tissues of the fasted animal of metabolites which favor the activities of microorganisms. In fact, it has been found

TABLE I.—EFFECT OF FASTING VS. CHRONIC UNDERNUTRITION ON MOUSE TUBERCULOSIS

Sherman Diet	*Weight Gain‡ (grams)*	*Cumulative number of mice (out of 10) dead at* 4 weeks	5 weeks	6 weeks	7 weeks	8 weeks	9 weeks	10 weeks	11 weeks
ad lib	12.5	0	1	1	2	3	3	4	4
1 period of fasting*	10.5	1	3	3	4	4	5	7	7
2 periods of fasting**	7	2	4	4	5	6	7	9	10
3.5 gm. daily†	1	0	1	1	1	1	3	3	5

* Food withdrawn once for 30 hours 5 days after infection; otherwise diet given ad lib.
** Food withdrawn twice for 30 hours 5 days and 12 days after infection; otherwise diet given ad lib.
† This corresponds to two-thirds of normal food intake.
‡ Average (in grams) per uninfected, control mouse over a period of 6 weeks.

TABLE II.—EFFECT OF FASTING ON SUSCEPTIBILITY OF MICE TO INFECTION WITH STAPHYLOCOCCUS AUREUS OR KLEBSIELLA PNEUMONIAE

Infection	*Diet*	*Drinking Fluid†*	*Deaths Per Cent*
Staph 0.1 ml i.v.	ad lib	water	5
" " " "	Fasting*	water	75
" " " "	"	citrate	75
" " " "	"	lactate	35
Klebs. 10-3 ml i.v.	ad lib	water	0
" " " "	Fasting*	water	75
" " " "	"	citrate	100
" 10-4 " "	"	water	60

* Animals fasted for 24 hours before, and 12 hours after infection; food (pellets) otherwise supplied ad lib.
† Supplied throughout period of fasting and until end of experiment.

TABLE III.—EFFECT ON MOUSE TUBERCULOSIS OF CITRATE, GLUTARATE, LACTATE, AND ALCOHOL

Pellets ad lib Drinking fluid	*Cumulative number of mice (out of 10) dead at* 3 weeks	4 weeks	5 weeks	6 weeks
0.8% NaCl	0	1	5	10
2% Na citrate (pH6.0)	2	7	9	10
1% Na glutarate (pH6.0)	1	7	9	10
2% Na lactate (pH6.0)	0	0	3	7
5% alcohol in saline	0	2	7	9

TABLE IV—EFFECT OF DINITROPHENOL AND THYROID EXTRACT ON MOUSE TUBERCULOSIS

Pellets ad lib		*Cumulative number of mice* dead at*		
Drinking fluid containing (per cent)		*4*	*5*	*6*
Dinitrophenol	*Thyroid Extract*	*weeks*	*weeks*	*weeks*
0	0	1	5	10
0.0025	0	2	4	6
0.005	0	4	7	10
0.01	0	4	7	10
0	0.003	2	3	7
0	0.01	4	8	10
0	0.03	10	—	—

* Out of 10 mice.

that the death of tuberculous mice can be accelerated in a striking and consistent manner by adding to otherwise satisfactory diets certain metabolites such as sodium butyrate, citrate or glutarate; alcohol or lactate have no similar infection-enhancing effect, even when added to the diet in higher concentration[37] (Table III). It is of interest that mice can also be rendered more susceptible to infection with Salmonella typhimurium by injecting them at short intervals of time with solutions of sodium citrate or other metabolites.[39]

Like malnutrition, endocrine disturbances have long been implicated in susceptibility to infectious diseases. The infection-enhancing effect—in man and animals—of treatment with large amounts of cortisone has been described so often as to need no further mention (reviewed in references 11 and 12). Evidence has also been published that estrogen activates tuberculosis in rabbits and guinea pigs,[40] and thyroxine in mice.[41] Extensive experimentation in our laboratory has revealed that mice receiving daily in their diet amounts of thyroxine or of dinitrophenol sufficient to retard their normal weight gain exhibit an unusually high susceptibility to infection with tubercle bacilli and staphylococci (Table IV). The infection-enhancing effect of these metabolic stimulants is not immediate; it requires at least several days before becoming manifest.[37, 38]

The findings in experimental animals leave no doubt that one can at will decrease resistance to infection by simple manipulations of the dietary regimen or by causing certain metabolic or humoral disturbances; but though these effects are clear, their mechanism is very obscure. Acceleration of the death rate of infected animals could be the result of several independent causes which can be classified under at least three headings: a) The infection-enhancing substance or procedure might bring about in vivo an environment more favorable to the multiplication or survival of the infectious agent either by causing a depletion of the tissues in some growth inhibitor, or an increase in some growth accelerator. b) It might create conditions which change the infectious agent qualitatively, allowing it for example to express a wider range of its toxic potentialities. c) It might render the infected animal more susceptible to the effect of these toxins.

Before mentioning some of the specific reactions which one can assume to play a part in the enhancement of infection, it is important to emphasize that any disturbance, nutritional or metabolic, sets into motion a large number of complex processes with a multiplicity of ill defined secondary effects. These, often far removed from the initial disturbance, certainly involve in many cases various components of the endocrine system. Many of the observed cases of aggravation of disease might be due for example to an overproduction of cortisone. Hormones in their turn can indirectly bring about profound changes in the physicochemical characteristics of the in vivo environment. Thus cortisone, by reducing the inflammatory reaction, is likely to decrease the production of lactic acid at the site of the lesions. Or again hormones, through their control over the various inhibitors and activators of tissue proteases,[42] probably affect the stability of fibrin and collagen structures and thus modify the rate of exchanges between the lesion and the general body fluids (reviewed in reference 20). One might postulate also an effect of physiological disturbances on the activity and concentration in serum of the recently discovered properdin, a globulin which appears capable of inactivating some viruses and gram negative bacilli.[43] These few examples suffice to illustrate the complexity of the secondary effects through which physiological disturbances might affect the infectious process.

Among the responses of the total organism to the procedures capable of increasing susceptibility to infection there are some metabolic phen-

omena which may have a direct bearing on the behavior and fate of microorganisms in vivo. It has long been known for example that one of the first and most dramatic results of starvation is the utilization of the glycogen reserves of the body. Treatment with thyroxine or with dinitrophenol also brings about depletion of the glycogen stores, probably by interfering with the phosphorylation reactions essential to the synthesis of this polysaccharide.[44, 45] There is evidence on the other hand that phagocytic and other tissue cells depend upon glycogen for their metabolic activity, and probably derive their energy through the production of lactic acid by glycolysis.[46, 47] Thus it is conceivable that acute starvation, as well as administration of thyroxine or dinitrophenol, may activate infection indirectly through an influence on phagocytosis and on the accumulation of lactic acid in inflammatory areas.

Starvation has of course many other metabolic effects. Like uncontrolled diabetes, it brings about overproduction or accumulation of acetone bodies, particularly in its early phase. Since, as already mentioned, a number of keto acids can stimulate bacterial growth, and furthermore counteract the antibacterial activity of lactic acid, it seems not impossible that the increased susceptibility to infection often associated with diabetes and starvation is due in part to the ketosis brought about by these metabolic states.[20, 25, 37] The more severe course of salmonellosis in animals treated parenterally with citric acid[39] and of tuberculosis in mice receiving either citrate or glutarate in their diet[37] (Table III), can be cited to illustrate the profound effect exerted on infection by presenting the tissues with abnormal amounts of certain metabolites.

* * * *

Although the precise mechanism through which nutritional, metabolic, and hormonal disturbances affect the infectious process can be discussed only in terms of unproven hypotheses, some biological consequences of the phenomenon appear in a clearer light. We have already mentioned that withdrawal of food for only twenty-four hours can shorten in a dramatic manner the survival of mice infected with tubercle bacilli, staphylococci or Friedländer bacilli[37] (Tables I and II). Very recent observations have revealed furthermore that this effect obtains even in animals which have been vaccinated (with BCG in the case of tuberculosis, with the specific polysaccharide antigen in the case of Fried-

TABLE V.—COMPARATIVE EFFECTS OF VARIOUS DIETARY REGIMENS ON MOUSE TUBERCULOSIS AND ON WEIGHTS OF UNINFECTED ANIMALS

Percentage composition of diets					*Weight gain† (grams)*	*Cumulative number of mice* dead at*		
Skim milk	*Wheat Flour*	*Cerelose*	*Peanut Oil*	*Citrate*		*3 weeks*	*5 weeks*	*7 weeks*
4	45	30	20	—	3.8	0	1	2
4	45	50	—	—	3.0	1	7	10
4	45	40	—	10	0	3	8	10
34	65	—	—	—	8.8	0	0	4

* Out of 10
† Average per mouse over a period of 3 weeks.

länder infection). Thus, it is plain that a metabolic disturbance even very transient, can greatly increase receptivity to infection, a fact which may have far reaching epidemiological significance. Indeed, certain unsolved problems of epidemiology could be viewed in a new light if it were a general truth that the manner in which a given individual can deal with infectious agents varies widely from day to day independently of his immunological state and merely as a result of physiological stresses. The belief that certain diseases are more likely to be contracted if there is prolonged exposure to a source of the causative microorganism—for example in leprosy—might signify that the body is receptive to this agent only under certain transient physiological states. Contact and receptivity may be rarely coincidental.

It is likely, as we have emphasized, that the increase in susceptibility caused by the temporary deprivation of food is not the result of nutritional deficiencies as ordinarily thought of, but rather the consequence of the abnormal utilization or accumulation of some metabolite. If correct, this conclusion makes it doubtful that the criteria commonly used for the study of nutritional factors can serve to evaluate dietary regimens with regard to resistance to infectious diseases. The results presented in Table V illustrate for example that one cannot predict the effect of a given dietary regimen on susceptibility to tuberculous infection from its effect on the weight curve of uninfected animals. Many other facts point to the conclusion that the nutritional factors essential for growth and reproduction are not necessarily the ones most

important in determining receptivity to infectious agents and resistance to the diseases that they cause. These two latter properties are concerned, not with what is good for the host considered as an isolated system, but rather with the factors which control the interrelationships between host and parasites. It is even possible that receptivity to infection, and resistance to disease, are two different characteristics and are controlled by independent mechanisms.

In summary the metabolic determinants of resistance to infectious agents almost certainly differ from, and may even be independent of, those which control normal physiological behavior. Their identification demands the development of new experimental techniques, based on consideration of the factors which determine the multiplication and survival of microbial agents in vivo, the production of toxic substances, and the host response to the microorganisms and their products.

Ever since the formulation of the germ theory, the emphasis in the control of infectious diseases has been placed on a direct attack on the microbial parasites—by means of drugs, sera, vaccines, or public health measures. A new phase of the germ theory may well unfold itself if it becomes possible to identify the metabolic factors which permit so many individuals to harbor without manifestations of disease, microorganisms endowed with pathogenic potentialities. On the basis of this knowledge, it might some day become possible to design techniques of metabolic control that would help man live at peace with microbial parasites. Many of these, after all, constitute an inescapable part of his biological environment.

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CURRENT METHODS IN THE TREATMENT OF TUBERCULOSIS*

The Second Harlow Brooks Lecture

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THE general improvement in the picture of tuberculosis in many countries in which facilities and trained personnel are available to cope with it may be interpreted, at least in part, as evidence of the greater efficacy of treatment. In the United States the lowering of the death rate from this disease to a level of 12.6 per 100,000 in 1953, which represents about 6 per cent of the rate prevailing in 1900 and a drop of 22 per cent in one year, certainly indicates the increasing success of measures for control. Among these a direct reflection of the better results of treatment is the declining death rate in tuberculosis hospitals and sanatoria. For many years and as late as the 1940s this averaged close to 20 per cent of all patients departing from these institutions each year;[1] in 1953, in New York tuberculosis hospitals, it was 7 per cent. However, 29 per cent of the patients departing from these hospitals in 1953 left against medical advice, compared with 20 per cent in 1950.[2] In many cases this is a consequence of the early and marked symptomatic improvement under chemotherapy which often deceives patients into thinking wrongly that the disease is healed. On the debit side, it must also be recognized that in this and other countries the tuberculosis death rate has decreased relatively little among elderly men, a relatively high rate still prevails among the non-white members of our population, the registration of new cases has not declined greatly, and the chance of recovery is materially less for a patient of small means than it is for his economically prosperous brother.[3] Tuberculosis continues throughout the world to be a major threat to health and life. It is clear, therefore, that therapy is just one means of attack and that its success, aside from its own intrinsic merits, depends also on many related factors.

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The approach to treatment is directed by three major considerations: The biological characteristics of the tubercle bacillus, particularly its great faculty of long survival in the tissues of the body, the unique form and composition of the lesions which it causes, and the natural resistance of the host. As to the bacillus, there is abundant evidence that during the development of lesions there is a great proliferation of the microbes while others die and undergo lysis. Under natural conditions of healing, particularly after fibrosis and calcification are well developed, some lesions become sterile but this usually seems to require a number of years; in others the bacillus survives and remains capable of causing relapses after several decades. Under the influence of chemotherapy with various combinations of streptomycin, isoniazid and para-aminosalicylic acid, administered for a period of months, there is clear-cut evidence not only of inhibition or suppression of bacterial proliferation but also, in many lesions, of profound modification of the biological properties of *some* of the bacilli so that they are no longer capable of growing on the usual artificial culture media or of causing progressive disease in guinea pigs. It has also been found, among bacilli obtained from patients treated with isoniazid, that such attenuation of virulence occurs as the bacilli first manifest resistance against the further action of the drug. These phenomena suggest that some of the bacilli may be killed rather rapidly by the treatment, but the question is still debatable and under investigation.[4-6] There are curious discrepancies since some patients, who yield these attenuated strains from their sputum, have been observed to continue suffering from progressive tuberculosis and later to die from it; furthermore, it has been found that some of these bacterial strains which fail to grow on ordinary media may be induced to do so by specialized techniques[7] and some which are relatively harmless in guinea pigs may kill mice.[6] The observations have stimulated new studies of bacterial metabolism and may well lead to identification of the mechanisms by which the specific drugs act. In view of the unsettled state of our knowledge and considering the frequency of failures of treatment and of relapses of the disease after the temporary success of treatment, we are obliged at present to work on the assumption that tubercle bacilli do survive in the lesions of patients, even after a few years of uninterrupted chemotherapy, and that some of these organisms retain their virulence. A more sanguine view may become justified as new drugs and new regimens are tested and become available. The demonstration by Mc-

Dermott and his associates[8] that combinations of pyrazinamide and isoniazid may sterilize the tissues of tuberculous mice, if not those of human patients, gives reason for interest in this direction and possibly for hope. Unless and until a sterilizing therapy for human tuberculosis is discovered, treatment can be considered fully effective only when it leads to the establishment of conditions in the body by which surviving bacilli will be confined and thereby rendered innocuous for the remainder of the patient's life.

Aside from the durability of the bacillus living in an unfavorable environment, the character of the lesion which it produces, most often in the lungs, adds to the difficulties of therapy. Were this a simple inflammation like pneumococcal pneumonia, it might be expected to resolve completely, leaving no trace, but the pathological hindrance in tuberculosis is the invariable necrosis of tissue whenever the disease is of sufficient extent to cause illness. This familiar caseation has many implications. It is responsible through the processes of liquefaction and sloughing for spreading the infection by various channels. Examples are the contamination of the blood stream by the ulceration of such a lesion into a pulmonary vein and, much more often, the discharge of infectious pus into the bronchial tree and its connections, resulting in progressive involvement of the lungs, the larynx, the intestine, and other structures along the way. The cavity left in the lung is usually an omen of chronic disability and eventually of a fatal outcome unless it can be dealt with effectively by the various means of treatment. Likewise the partially healed solid necrotic focus, more or less encapsulated by fibrous tissue, becomes a refuge in which living tubercle bacilli may lurk for indefinite periods of time. Sometimes, because of an identifiable accident, but more often for reasons unknown, softening and liquefaction of the necrotic focus is resumed and the progeny of these organisms may emerge to initiate the relapse which is the familiar characteristic of the disease. Under prolonged chemotherapy, it has been demonstrated that the physical character of the lesion has much influence on the behavior of the tubercle bacilli; drug resistance becomes manifest earlier among those recovered from actively excavating lesions than it does among those from solid and almost encapsulated caseous lesions. The local biochemical factors which may influence these differences have been studied and discussed by Dubos[9] and his associates. Coping with the cavitary case remains the most difficult problem of treatment. Under the influence of

specific drugs, the walls of the cavity may be so transformed by fibrosis that the tuberculous elements are difficult to demonstrate; a cyst-like cavity is left and this is sometimes called "open healing." Tubercle bacilli often disappear from the sputum. This is a unique effect of chemotherapy, but not to be relied upon as permanent since the later relapse rate in these cases is high and diligent histological searches of the walls of resected cavities usually reveal at least small remnants of tuberculous tissue. Early symptomatic recovery under treatment is much to be desired but it is also obviously important to judge the implications of the remaining lesions and to extend treatment for their permanent control or eradication, if possible.

Probably no available treatment of tuberculosis would be efficacious were it not for the natural resistance of the human body against the infection. The nature of resistance is poorly understood and we have no accurate means of measuring it; its adequacy is judged best after the event, rather than before it. Despite this, it is the major defense on which every patient must rely to recover from tuberculosis and to remain well. Resistance seems to fluctuate, sometimes rapidly; it declines during sustained periods of excessive physical or emotional stress and rises when all is serene and restful; hence the basis of rest treatment. Among the many factors which influence resistance a few may be identified statistically in groups of the population, such as age, sex, and occupational conditions, and others suggest themselves in the individual case, such as associated diabetes and malnutrition.

Of all the tangible factors which determine the outcome of a case, the most important are the stage and clinical character of the disease at the time of diagnosis and the promptness with which treatment is instituted. Far advanced bilateral pulmonary tuberculosis always has had a dismal prognosis under any form of treatment, and long survival is exceptional. Today, the possibility of symptomatic benefit is much better and life may be greatly prolonged in many cases. At the other extreme, early pulmonary tuberculosis, if diagnosed while its extent is still limited to small areas, usually responds well to rest treatment alone indicating the relative adequacy of natural resistance. However, in some of these cases relapses and deaths do occur, particularly if the disease is not arrested within two years after its inception.[10] With chemotherapy, rest treatment, and surgical resection of the lesion in refractory cases a permanent recovery rate close to 100 per cent probably can be anticipated.

Methods of treatment are various, offering the possibility of many choices according to the needs of the individual patient. The use of rest to enhance natural resistance and to exert certain favorable mechanical influences on the local lesion is indispensable during the early months. With the use of chemotherapy and surgery, the duration of disability is materially abbreviated in many advanced cases, but there is still a considerable relapse rate which compels many of these patients to resume resting. In the early minimal case, however, the prospect of permanent recovery is so good that a long initial period of rest and graduated activity amounting to one to two years, is usually advisable before full time work is resumed. The optimum degree of rest and the means of obtaining it varies according to the circumstances; confinement to bed does not always mean absolute rest. The objective, of course, is maximum relaxation and relief of tension since this has been shown empirically to favor the best response. How this is to be achieved is a matter of judgment and trial in each case.

With the exception of apparently stable and healed lesions the specific drugs are now employed in virtually all cases of tuberculosis. The choice of drugs and regimens and the duration of administration is determined individually; it is desirable to continue until the signs of local healing give reasonable assurance that future exacerbations will not occur. Judgment is very difficult, particularly with respect to future potentialities of arrested lesions, and in many instances the adequacy of treatment can be determined only by a period of close observation and follow-up.

Surgical methods for the control or elimination of severe disease have been perfected to a remarkable degree and are employed in many carefully selected cases. The favorable results of these operations depend greatly on the preparation of the patient, usually by a lengthy period of treatment and the recognition of the time when conditions are optimum for avoiding operative and postoperative risks. Surgical measures to control pulmonary disease by collapsing the lung, such as the classical thoracoplasty or some modification of it, are effective in two-thirds to three-quarters of patients selected for such procedures,[11,12] and these figures probably will be improved when, in addition to rest, chemotherapy is also used. Collapsing the lung by artificial pneumothorax, which checked the disease in many cases,[13] is employed much less often since chemotherapy became available, largely because of the necessarily

long duration of the treatment and the incidence of pleural complications. Simultaneously, there has been an upward surge in many institutions of the use of pneumoperitoneum, although few depend on this alone and many are skeptical of its value except in some bilateral cavitary cases.

Of the many drugs which exert an inhibitory action against the proliferation of tubercle bacilli, those which have had the most thorough testing are streptomycin (and dihydrostreptomycin), isoniazid, and para-aminosalicylic acid. The sulfones and amithiozone also have been well studied but because of their limited effectiveness are not widely used. Pyrazinamide is effective in human subjects for at least short periods of time, particularly when administered with other drugs, and may well prove in the future to be a valuable agent; it may cause toxic hepatitis. Viomycin possesses the virtue of exerting active bacteriostasis when administered to patients whose tubercle bacilli are found to be resistant against other drugs, such as streptomycin. However, viomycin often causes toxic effects, particularly on the eighth cranial nerve, which necessitates great caution in its administration.[14] Other drugs which seem to hold promise are also under investigation. Principally because of the necessity of lengthy periods of treatment and the obstacle of drug resistance which usually becomes manifest within relatively short periods of time (two to twelve weeks) after a single drug is administered daily, it becomes necessary to devise means of delaying such manifestations, and this is accomplished in part by the administration of two or more drugs simultaneously.

The rationale of treatment of tuberculosis depends greatly on an understanding of its evolution, its behavior in particular sites, and the various mechanisms of healing. The most complex and difficult problems are encountered in disease of parenchymal organs, such as the lungs and the kidneys. In the lungs, the early lesion is exudative and pneumonic and this type of reaction is a constant component of all acute and extensive lesions and, in more or less mild degree, also of many chronic lesions. In early and acute pulmonary disease, even before symptoms become severe, there are important potentialities either of rapid and marked resolution of inflammatory exudate or of necrosis not only of the exudate which has been poured into the alveolar spaces but also of the pulmonary tissue itself. Necrosis and excavation in acute cases may occur extensively within several weeks or months, while in more chronic

cases the process may be very slow and in time may come to a halt. Destroyed tissue is never restored to normal and at best can only be replaced by fibrous organization. The importance of this in the acute case is so vital that one may digress to point at the grievous error of treating early tuberculous pneumonia with penicillin on the mistaken assumption that the cause is the pneumococcus. The loss of even several weeks of time in instituting proper therapy may spell the difference between extensive resolution and extensive destruction with all the implications of each. The immediate problem in any case of active disease is to favor suppression of the infection as promptly as possible and it is at this point that chemotherapy exerts its greatest effects. The rate of its action varies according to the severity of the case. In symptomatic acute disease of several weeks duration prompt critical lowering of the fever often occurs, and this may be accompanied by a rather dramatic improvement of the general condition including a gain in weight. Simultaneously, the output of sputum may be rapidly reduced and in several weeks or months may be inconsequential. This, together with the disappearance of tubercle bacilli from the sputum or gastric washings, reflects the local effects of bacteriostasis, namely, a diminution or cessation of exudation through and from the wall of cavities. Its importance is self-evident when it is recalled that continuing purulent bacillary discharges from cavities are responsible so often for the spread of the disease. Accompanying such effects there is almost always a rather rapid resolution of surrounding exudate which has not yet undergone necrosis and frequently a diminution of the size of cavities. In very acute caseous pneumonia in which the resistance of the patient inferentially is assumed to be relatively low, the response to chemotherapy and bed rest often is much slower. High fever may not abate for six or eight weeks and the diminution of other symptoms is also very gradual. In still other cases of very extensive bilateral disease with severe symptoms, the effects of the best available treatment are unavailing and the patient may die in a few weeks or several months. In more chronic cases with mild symptoms the response to chemotherapy is more consistently favorable, but, because of areas of necrosis and fibrosis the anatomical regressions, best demonstrated by roentgenograms, are usually less striking.

In any event, after symptomatic control has been achieved and maximum regression of the lesions has occurred, the problem of assessing and

interpreting the implications of residual lesions remains. These may be represented by rather clean fibroid cavities which are dried out, more or less inspissated solid caseous lesions which may be enclosed in some fibrosis, and small foci which may be almost completely transformed into fibrous tissue. The last are likely to remain healed but, as stated, the other two have a great tendency later to flare up into renewed activity causing further extension of the disease and clinical relapse. Such residues, if not very large, may slowly regress under further rest treatment and chemotherapy continued in some cases for another one or two years. Finally, small cavities may be completely obliterated and all fibrocaseous lesions may seem to be well circumscribed and arrested. Under favorable conditions of living, the prognosis for permanent recovery is good but because of viable bacilli contained in the lesions, vigilance must be exercised throughout the patient's life to detect the slightest evidence of recurrence. Larger lesions of a cavitary or solid fibrocaseous composition are looked upon with apprehension even though symptomatic recovery may have been complete. The solid lesion may remain quiescent indefinitely but its tendency, even after a lapse of a few years, to undergo liquefaction, sloughing and discharge of infection into the bronchial tree is well recognized. The threat is greatest when the lesion is known to have sloughed previously, when it is more than one or two centimeters in diameter, when its origin is relatively recent and when it occurs in young people. Because of the multiplicity of factors involved, the outcome cannot be predicted with certainty. Chemotherapy and some form of general treatment may be continued pending observation but the finding of tubercle bacilli by cultures of the sputum or gastric contents after a year or more of such treatment is a sign of imperfect healing and a liability of the lesion to progress again. Then one may be so convinced of the threat that surgery may be decided upon for removal of the focus.

It has not been shown that collapse of the lung by thoracoplasty or artificial pneumothorax materially influences the future of these solid caseous lesions. If surgical treatment is indicated, therefore, resection is favored. The time may be appropriate after symptoms have been relieved and the lesion has become stabilized, isolated and well circumscribed; depending on its original appearance, this may require six months or more. Notable success has been achieved by skilled surgeons in removing these lesions by resection of lobes, segments or sub-segments, thus conserving healthy or less involved tissue. There is a risk of complications

such as pleural fistula and tuberculous empyema and the incidence of these varies according to the selection of cases and other circumstances.

In the case of persisting pulmonary cavity the prospect of relapse on discontinuing chemotherapy or because of the development of drug resistance is very great and it becomes necessary, if possible, to deal with the case surgically. Collapse of the diseased part by thoracoplasty or some similar procedure may be possible if the anatomical relations are suitable; healing may be adequate and permanent after these relatively clean fibrotic cavity walls are collapsed and brought together. This may be the procedure of choice when the disease has been extensive and residual fibrocaseous lesions are widely distributed, but if the severely destructive disease has been confined to one lobe it is preferable, after due preparation by rest and chemotherapy, to resect the lobe totally, and this may be followed by partial thoracoplasty to reduce the vacant space.

Bilateral resectional surgery is occasionally carried out, particularly for the removal of localized lesions which threaten to be sources of future relapses but the range of its usefulness is narrow.

Owing to the unfortunate fact that most cases of pulmonary tuberculosis on first diagnosis are moderately advanced or far advanced, the immediate results of treatment in many are little more than palliative. Extensive acute bilateral tuberculous pneumonia which ordinarily would run its fatal course within a few months may be arrested and the patient's life may be prolonged, but the disease is not improved beyond the point of chronicity. These cases, together with chronic bilateral cavitary disease which is so frequently encountered at the time of diagnosis, present most difficult problems. With initial chemotherapy and rest treatment the symptomatic recovery may be striking but the future course is likely to be precarious. The extent of destruction of tissue may be so great and widely distributed that surgery has no place. It has been proposed in these cases that chemotherapy might be continued with some effect throughout the remainder of the patient's life. It is known that some of these patients may live for several decades, provided they accept what is virtually a life of chronic invalidism. With chemotherapy such a state may be more bearable since symptoms may be more or less controlled, but in many cases the prospect is faced that progressive fibrosis will encroach upon respiratory function, producing strain of the right heart and rather miserable disability from this cause; furthermore,

while in some cases chemotherapy may be continued with effect for four or five years, it must be recognized that no combination of drugs has been proved to be effective indefinitely. Many of these patients will join the army of chronics which is considered to be the main source of infection in the community. The possibility has been recognized and cases have been documented in which a primary infection has been found due to drug resistant strains of tubercle bacilli presumably acquired from such previously treated patients. Thus it is seen the complexity of the problem increases. The obvious solution is to apply the known and effective means of diagnosis and treatment before the disease has advanced to a vast and irreparable extent.

The nature of tuberculosis of the kidney is analogous in some respects to that of the lung, especially in not causing symptoms until necrosis and sloughing have occurred. Chemotherapy may be prompt and impressive in its immediate effects and, depending somewhat on the severity of the tissue destruction, the urine may be sterilized within a few weeks or months. But here, as in the lung and other parenchymal structures, the necrotic and excavating lesion may continue harboring viable organisms which may lead to exacerbations even after a long period of quiescence. It is recognized, therefore, that symptomatic improvement is only one criterion, that prognosis hinges largely on the extent of tissue destruction, and that in many cases nephrectomy or partial nephrectomy may be necessary to assure the best results.[16] With prolonged chemotherapy for advanced bilateral cases, symptomatic relief may continue for some years but the ultimate duration and degree of this remains to be determined.

The influence of the different structures and relations of tuberculous tissues is further exemplified by the behavior of the disease in the mucous and serous membranes. Under natural conditions the lesions have a much greater tendency to heal themselves than those, for instance, in the lung or kidney, and this difference is even more striking under the influence of chemotherapy. Lesions in the mucosa of the larynx, intestine and bladder recede rapidly and are soon covered by a regrowth of the epithelium. Symptoms often subside with remarkable rapidity. The explanation relates largely to the fact that such lesions, when they have gone on to ulceration, cast off their necrotic elements readily and rapidly, leaving only shallow defects. Repair is not hindered by the presence of large necrotic elements and proceeds rapidly and effectively.

In acute generalized miliary tuberculosis which, because of the overwhelming infection, usually runs its fatal course within three or four months the possibilities of recovery under chemotherapy are favorable if the diagnosis is made early and treatment is initiated promptly. The progress of the myriad tiny lesions is arrested and most or all of them eventually may be converted to fibrous tissue. It is conceivable that many of these minute lesions may actually be sterilized; in contrast the same amount of tuberculous tissue concentrated into one or several massive and confluent pulmonary lesions could not be expected to respond so favorably. Relapses occur after recovery from generalized miliary tuberculosis but the exact mechanism has not yet been demonstrated in many cases. It is possible that exacerbation in some cases may be due not to a reactivation of the miliary lesions but rather to a renewed softening and sloughing of the necrotic lesion in the lung or elsewhere which was the original source of the dissemination through the blood stream. If generalized infection is not diagnosed early and original treatment is not so effective, it may be expected that the residual lesions in various tissues of the body will have gone on to necrosis before subsiding and that bacteria may survive in these numerous foci for long periods of time. There is good evidence, for instance, to indicate that relapses of tuberculous meningitis after treatment may be due to such latent lesions remaining in the cortex of the brain.[10] These peculiarities of the pathology of tuberculosis have been repeatedly stressed by Medlar and are major considerations, aside from the natural resistance of the host and the antibacterial effects of the drugs. Obviously, therefore, each case must be judged according to an estimate of all these factors, realizing that the clinician is handicapped by many limitations of our knowledge. In practical terms one must consider not only the immediate response to treatment but also the probable ultimate behavior of the lesions and the probable requirements in terms of prolonged chemotherapy, surgical treatment and rest treatment. At best this is difficult and in recently developed cases a period of observation of at least a few months may be necessary before the long term prognosis can be estimated.

The variety of regimens of combined chemotherapy, that is, two or more drugs administered simultaneously, is great and may be expected to increase. A number of these have received broad and intensive study under the auspices of the United States Veterans Administration, Army and Navy Hospitals, the United States Public Health Service, and the

British Research Council. These agencies have made unique contributions which assuredly will be of permanent value in this field. The complexities are great, long periods of study are required, and it may be said that our present knowledge in many respects is only tentative. To illustrate the development of the regimens, it has been learned that the toxicity and disagreeable side effects of streptomycin can be avoided or minimized by limiting the dose to one gram daily or, preferably, to one or two grams every two or three days. Such low dosage, particularly in very active cases of tuberculosis may detract from the desired therapeutic effect but this objection is overcome and the effect is enhanced by the addition, for instance, of para-aminosalicylic acid in doses of 12 to 15 grams daily. The other advantage of the combination is the delay of bacterial drug resistance. The delay usually lasts for at least four months and in some cases much longer, a quality which is essential in view of the stubbornness and duration of tuberculous disease. Other regimens include isoniazid-para-aminosalicylic acid, isoniazid-streptomycin, and isoniazid-streptomycin-para-aminosalicylic acid. Their relative merits are still under study but their therapeutic effects approach each other rather closely. With any tested combination it has been shown that, while drug resistance may be delayed, it cannot with assurance be prevented eventually. Realizing as we must, therefore, that late exacerbations of tuberculosis may occur after initial recovery, there are reasons for withholding for possible future needs one or more drugs to which the bacteria have not become resistant. Since the two most potent drugs are streptomycin and isoniazid, many feel that only one of these should be used during initial treatment in combination with a less effective drug such as para-aminosalicylic acid. Such consideration may have to be thrown to the winds when the severity of the disease is extreme. Thus, in cases of meningitis and generalized miliary tuberculosis there is no hesitation in administering 2 grams of streptomycin intramuscularly daily with large doses of isoniazid (8 to 10 mg. per kilo per day) by mouth. This regimen has proved superior to others although some physicians like to add para-aminosalicylic acid also. A regimen of these three drugs might be expected theoretically to be superior to combinations of only two and there is some evidence that drug resistance is longer delayed by such a triple regimen and that the therapeutic effect may be more certain.[17] This varies undoubtedly with the urgency of the case and probable needs in the remote future; further study is required. In any

event it has been found important to continue a selected regimen consistently and without interruption until symptoms have been controlled and then usually for a further period of many months during which it may be anticipated that the sustained antibacterial effects will permit the repair of local lesions to proceed without interruption. During this time it may be wise to reduce the dose or frequency of administration of streptomycin to lessen the risk of its toxicity; there need not be much apprehension about toxic effects from isoniazid. Except for a judgment based on the clinical features of the case, the character of the lesions and the general experience to date, there is no precise way of determining when healing is adequate and chemotherapy may be discontinued. A course of six to eight weeks has seemed to be sufficient in some pulmonary cases but this is exceptional and, as a rule, the course is calculated in terms of six to twelve months, often longer. In other cases, particularly the advanced cavitary cases, prompt relapses have occurred at the conclusion of courses of treatment lasting for a couple of years. In the case of meningitis there is satisfactory evidence to indicate the wisdom of continuing combined therapy for at least a year after clinical recovery and the restoration of the spinal fluid to normal. After surgical operations, such as the resection of pulmonary lesions, chemotherapy is usually continued for at least six months to help insure the healing of the operative defect and to control minor lesions which cannot be reached by operation.

It would be a great advantage, of course, if a single inexpensive drug could be administered by mouth producing effects equal to those of combined therapy. Deuschle and his associates[18] have demonstrated the merits of isoniazid for this purpose and believe it may be so employed in special circumstances. The results will vary undoubtedly according to the severity of the disease. In some instances the favorable clinical effects may continue after the bacteria become resistant to isoniazid, and this is also true of other drugs. On the other hand, studies by ourselves and others have revealed unpredictable disadvantages recognized in failures to clear the sputum of tubercle bacilli and a greater frequency of eventual clinical relapse.

The great advantages of chemotherapy have had the expected effects of renewing interest in the possibilities of home care and of reducing the period of disability. As a consequence, many hospital beds have been evacuated. Matters are confused because of the uncertain durability

of early symptomatic recovery, the temptation of the patient to gamble and return too soon to work, and the pressure to reduce the expense of hospital treatment. The soundness of this trend will be determined only by limited and carefully organized studies since in some localities the situation is almost chaotic and the expectation of obtaining reliable information is nil. The possibility of a patient's losing his chance of permanent recovery by hasty decisions and undue reliance on chemotherapy is becoming evident in some cases. There has also been some apprehension regarding an increased dissemination of the infection among the population by patients discharged from hospitals before their disease is arrested. During the early years of the last war many tuberculosis hospitals in England were evacuated and patients were sent home. Numbers of these patients experienced an aggravation of disease and died, but the more alarming phenomenon was a sharp rise in the incidence and fatalities of the disease among children,[19] obviously due to their infection through close contact. During the present trend away from hospitals and toward treatment in the home, office and clinic, such results have been observed only in isolated instances. In New York among children under five years of age, 30 deaths from tuberculosis of the meninges and central nervous system were reported in 1941, and 37 in 1942, while despite the increase of children in our population there were only 24 such deaths in 1951 and 25 in 1952.[20] This index of communication of the infection seems to show that the current trend has not had dire effects generally. However, this death rate is no longer as meaningful as it once was since some patients in 1951-52 recovered from meningitis under chemotherapy. On the contrary, there is an impression, because of the frequent effect of chemotherapy in reducing the output of sputum, that the mass of infection disseminated in the community is diminishing. However, expectoration will recur in many poorly treated and poorly healed cases; some patients are already returning to hospitals on this account. Therefore, criteria are needed for advising the discharge from hospitals of patients still requiring treatment. In the Chest Clinic of Bellevue Hospital a systematic study of this problem is being conducted and this includes a survey of the home conditions to which the patient must return. It seems wise for the great majority of patients with active disease to undergo an early period of treatment and observation in a hospital in order to initiate treatment on a sound and safe basis and to evaluate their future prospects. The long

term plan of treatment may then be foreseen; the patient may be informed accordingly and may receive the education which is such a necessary element of his recovery.

In summary, the current methods of treatment of tuberculosis are more certain in their early favorable effects than those which were previously available. Bacteriostasis is exerted more promptly in active tuberculosis by chemotherapy than by the rest cure alone and early regression of the lesion, particularly resolution of inflammatory exudate, is accelerated impressively. The essential mechanisms of healing are not altered by chemotherapy and in no case can it be assumed that all, if any, of the lesions are sterilized. When tissue destruction has been extensive such healing is very undependable, and surgical treatment is often advisable. The field of surgical treatment has been widened since the introduction of chemotherapy and its effectiveness has been greatly improved. The selection of chemotherapeutic agents and regimens varies according to the site of the lesion and its physical character, the acuteness of the disease and the natural resistance of the patient. While permanent recovery is now more assured in many cases, the period of time required for initial treatment may not be greatly reduced. The trend away from hospital treatment is premature in many cases although treatment in the clinic and at home has a greater place than previously. The incidence of relapses is influenced, not only by medical treatment, but also by the understanding and cooperation of the patient and the circumstances which permit him to follow sound advice. The key to successful treatment is still early diagnosis and prompt action. There is ample room for improvement of methods of treatment and great need of further research in tuberculosis.

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CURRENT CONCEPTS IN THE MANAGEMENT OF ASTHMA, EMPHYSEMA AND CHRONIC PULMONARY INFECTIONS

*Transcription of a Panel Meeting on Therapeutics**

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Protocol

N.B. This case does not record in all instances the best or even good treatment. It is presented for purposes of discussion.

Case Report

Male. Age, 65 years. Height, 5′ 11″. Weight, 145 lbs.

Past history. Childhood and early history negative. No allergies. Business executive, no occupational exposure. Tobacco—1-2 packs daily. "Cigarette cough" for twenty years, with a little mucoid a.m. sputum.

1945. Attack of "virus pneumonia." Slow recovery. Some wheezing, exertional dyspnea and mild asthma during attack and for four months following.

1946. Several attacks of "bronchitis." Domestic worries. Severe attack of asthma in March, lasting three days. X-ray showed emphysema, with bullae in R.U.L. P.X. Chest emphysematous. Low diaphragms. Decreased breath sounds. Heart normal.

1947-1951. Fairly well. Found to be sensitive to streptococcal protein, tomatoes, and house dust. Received desensitizing injections; also, during the winters, injections of stock "influenza" vaccine.

1951-1952. Increasing dyspnea, not able to climb stairs. To office only once or twice a week. Spent six weeks in Arizona, made worse by dust storms. Home and to hospital. P.X. Very dyspneic, gasping inspiration, prolonged expiration. Moderately cyanotic. Frequent cough, with thick purulent sputum. Irregular fever for ten days. The following measurements were made:—

	Normal (approximate)	*Patient*
Maximum breathing Capacity, lit./min.	90	25
Residual Air/Total Capacity ratio	0.30	0.60
Arterial Blood Oxygen Saturation, %	96	85
Arterial Blood CO_2 Content vols. %	50	58
Arterial Blood CO_2 Tension, mm.	40	52
Arm Venous Plasma CO_2 vols. %	60	72

X-ray: Bulla in R.U.L. larger, with mediastinal displacement. Some R.V. hypertrophy, with conus prominence. Bulla explored by needle, air removed. No improvement. Ganglionectomy considered, not approved. With antibiotic therapy, bronchodilators, intermittent oxygen therapy, patient improved. To remove the expanding R.U.L. bulla, an R.U.L. lobectomy was performed. After a somewhat stormy course patient improved, was able to leave the hospital on bronchodilator, antihistaminic, continued "prophylactic" oral penicillin, intermittent nasal oxygen.

1952. After five months on reduced ambulatory regimen he caught a cold, with fever and cough. This hung on, he developed progressive swelling of legs, increasing cyanosis, dyspnea, cough, thick sputum, was readmitted to the hospital. P.X. T. 102. P. 116. R. 22. Intense cyanosis, gasping asphyxial respiration. Heart enlarged to L and R, P2 accentuated, gallop rhythm. Dullness and moist rales at both bases, asthmatic resp. Liver to umbilicus, edema of legs and thighs. Hgb. 19 gms., R.B.C. 6.8 million, W.B.C. 12,600, p. 82 per cent. Respiration improved after mechanical suction. Arterial blood oxygen saturation 62 per cent, arterial CO_2 content 80 vols. per cent. Patient placed in oxygen tent, improved for 12 hours then sank into coma. Arterial oxygen saturation 93 per cent, arterial CO_2 content 100 vols. per cent. Removed from oxygen, given a mask respirator, was uncooperative, then placed in Drinker tank respirator. Improved, removed after 10 days. Treated by digitalization, mercurials, repeated phlebotomy, as well as bronchodilators, etc. Ambulatory after eight weeks. Arterial oxygen saturation 89 per cent, arterial CO_2 content 68 vols. per cent, Hgb. 16.5 gms., R.B.C. 5.8 million. Finally sent home on bed-chair regime, with same medications, using a pos. pressure respirator t.i.d. Did fairly well for three weeks, was able to go out in car for one hour a day, then one morning was found dead in bed.

MODERATOR RICHARDS: We are introducing a slight change in the approach today by the use of a protocol giving what we conceive to be not an average case but a very frequent type of clinical case that comes in for therapy in the general category of chronic pulmonary disease with pulmonary insufficiency. This particular individual had perhaps more than his share of misfortune as time went on but that offers us an opportunity for discussion. As indicated at the top of the protocol, the case does not record in all instances the best or even good treatment. It is presented for purposes of discussion and the treatment received will be commented on by the panel.

I will go over the case briefly stopping at various points along the way as aspects of therapy come up and discussion will then be continued by one or another member of the panel. At the end we shall hope to have time to consider questions from the floor, not all of them perhaps but as many as we can within the time limits.

Of course, "Current Concepts in the Management of Asthma, Emphysema and Chronic Pulmonary Infections," is a tremendous subject and we can cover only certain aspects of it this afternoon. I will start then with this particular case report, which I think is in all your hands. If not, there are extra copies available.

The patient is a man of 65, of average stature, somewhat thin for his height, with a past history not particularly contributory except for the use of tobacco and what he called a cigarette cough, with a little sputum. His first episode of any consequence according to our history occurred in 1945, which takes us up essentially to the present time when he had an attack of what he called virus pneumonia, with slow recovery, a little wheezing, some exertional dyspnea and mild asthma persisting for four months. The next year he was troubled again with bronchitis, had psychological worries, had a severe attack of asthma, this time toward the end of the winter, and his x-ray is recorded as showing emphysema with bullae in the right upper lobe. He had an obviously emphysematous chest, low diaphragms, depressed breath sounds, on physical examination, and a heart that was recorded as normal.

After these two episodes he did fairly well for about four years under treatment. He was found to be sensitive to streptococcal protein, tomatoes, house dust. He received desensitizing injections and during the winters, injections of what was called influenza stock vaccine, which I will leave to Dr. Sherman to define further and perhaps he will pick

up the discussion at this point and give us some indication of the principles of therapy in this particular condition, what is good and what is bad.

DR. WILLIAM B. SHERMAN: The use of anti-allergic treatment, so-called, is of value in chronic pulmonary emphysema only in proportion as asthma is the cause of the emphysema and strictly speaking, the anti-allergic measures might be considered a prophylactic measure in regard to the emphysema, attempting to lessen its progress by relieving the asthmatic symptoms rather than curing the emphysema which is already present. Occasionally when the results are unusually favorable some of what we may have thought was irreversible change in the lungs gradually regresses to some extent.

In a patient with asthma we believe that the allergic type of investigation is essentially always warranted in order to arrive at least at a tentative diagnosis of the cause of the asthmatic symptoms, whether this be inhalant allergen such as feathers and animal danders, or dust, or a food or whether the asthma is due to infection, which may or may not represent a true bacterial allergy. The presumptive diagnosis as to the cause, based purely on the history, is very often fallacious, so that at least a brief allergic investigation is probably warranted in every case. Very often we see patients who have asthma only with colds and the natural assumption is that the asthma is due entirely to the colds. However, on investigation it is not infrequently found that the respiratory infection is merely what you might call the last straw in tipping off the attack of asthma in a patient who is actually allergic to inhalant allergens to which they are constantly exposed.

In the present instance it is noted that the patient was approximately 58 years old at the time that the asthma was apparent and the asthma followed a respiratory infection. This type of case coming on after age 50 and with no past history of allergy is perhaps the least hopeful type of case from the standpoint of allergic investigation, particularly with regard to the hope of finding an extrinsic allergen to which the patient is sensitive. Asthma starting after the age of 45 years is due in at least 80 per cent of the cases to infection and not due to any extrinsic allergy. It is noted that skin tests were done and that the patient reacted to house dust. Now even at this age if the reaction to house dust is a definitely strongly positive reaction, I think that we are warranted in assuming that it may be one factor in the condition and treat him accordingly. He also

reacted to tomatoes. The reaction to tomatoes I feel is far less significant. If the patient is actually having asthma from eating tomatoes he would have to be eating them very frequently and in considerable quantities to play an important part in his condition. However, I do think that if there is any doubt about the situation that the matter of eliminating tomatoes from the diet to avoid the question would be a relatively small and probably justifiable procedure although we would hesitate to say that the reaction to tomatoes was in any way really a significant factor in his condition.

Finally, taking these in reverse order, he reacted to streptococcal protein. This test may sound superficially of interest in that there is a good deal of other information in the history later in the course of his disease which indicates that infection was an important part in his condition. Unfortunately the skin test with any available type of streptococcal protein is not a reliable index of whether or not patients' asthma is related to streptococci. If it means a nuclear protein such a proportion of the general population will react to it that it loses all significance.

Another type of streptococcal protein, of course, is the Dick toxin which is used to test for susceptibility to scarlet fever and here again obviously there is no relation between a positive reaction and the occurrence of asthma, so that we may as well from the standpoint of diagnosis disregard the reaction to streptococcal protein and we will have to base our decisions as to the importance of infection in his condition purely on the clinical course and observations.

To get a little bit ahead, in the history it will be noted that later on when he spent a considerable period in the hospital he failed to improve. In fact, he did rather poorly in the hospital. This in itself is at least a hint that the asthmatic condition was due in large part to infection that he was carrying into the hospital with him and keeping with him and not to the dust to which he was exposed at home because the hospital environment, if not entirely free of dust, at least has a very different type of dust so that he no longer would be expected to react so much to it.

Finally, on numerous occasions he was noted to improve after the use of antibiotics so that we may reasonably assume that infection played an important part in his condition.

As for the treatment, he received desensitizing injections which I think we can assume were house dust extract and these I believe were justified. Whether they actually influenced the course of his illness is

rather hard to say except to note that for a period of four years he apparently did rather well. He also received during the winters injections of stock influenza vaccine. This vaccine might be presumed either to mean the ordinary mixed bacterial vaccine, which is available from many drug firms or the influenza virus vaccine, which is derived from strains of influenza virus.

To speak first of the stock bacterial vaccine, because it is the more commonly used, it is very common practice among people treating asthma when they are giving injections of dust, feathers, pollens, or other antigens to patients who have a great many respiratory infections to add a certain amount of mixed bacterial vaccine to the other antigens, the hope being if the patient is hypersensitive to bacteria, this will tend to lessen his sensitivity and lessen the occurrence of bacterial asthma. In regard to this type of treatment all I will say is that there is no clear-cut, well controlled proof that it has any substantial effect on the course of bacterial asthma. There are numerous reports that it has a favorable influence and it has been very generally used but I would say that nothing that would be considered a conclusive statistical proof has yet been offered. While the patients are receiving such courses of vaccine, they almost always are also having a good deal of symptomatic treatment and from time to time antibiotics are given at the early signs of infection because they are under close medical supervision. How much of the benefit is due to the vaccine or how much is due to other measures, I think would be very difficult to say.

In regard to the influenza virus vaccine, it has been used to some extent in recent years in patients with infective type of asthma simply in the hope that by attempting to immunize to as many different respiratory infections as possible the course of the disease would be somewhat alleviated. Here again I don't think we can make any statement other than to say that it is a simple thing to add a series of injections. So far as known it does no harm and it is possible it will protect against a certain number of virus infections of the respiratory tract.

The other thing that might be considered in anti-allergic measures is anti-allergic drugs. Shall we take those up, Dr. Richards?

MODERATOR RICHARDS: I think we might take those up a little later. They will come up in the consideration of the physiologically directed therapy later on.

Are there any further comments from the members of the panel on

this particular aspect? We will come back to this phase again doubtless in the course of questions from the floor.

We may proceed then with the patient's course, downhill as it is from here on, and we find that through 1951-'52 he was troubled with increasing dyspnea, now quite severe. There was an attempt to change climate which resulted in no improvement, and he finally came into the hospital in a very dyspneic state, a state of severe pulmonary decompensation, so that he was gasping in his respiratory effort, cyanotic, had frequent cough with now a thick, purulent sputum and he was running an irregular fever. This brings up again the question of infection which Dr. Sherman touched on. We will see that the patient received antibiotic therapy as expected and I think we might stop at this point and consider that aspect which is now receiving increasing emphasis in many places, the factor of infection in prolonging or worsening these chronic states as they go on from one year to another. *I will ask Dr. Galdston if he will discuss this aspect for us.*

DR. MORTON GALDSTON: This patient, it has been pointed out, had a background of chronic bronchitis of many years' duration ending in a clinical picture as far as we have gone, of pulmonary insufficiency.

Concerning treatment of the bacterial infection, we might start with the earlier phase of this patient's history. One might conceive of having prevented his ultimate downhill course by early institution of proper antibiotic therapy or chemotherapy. In such therapy one should, wherever possible, be guided by the nature of the organisms that are present in the sputum. In the absence of an acute emergency indicative of immediate need of antibacterial therapy, one can generally safely wait twenty-four or forty-eight hours, if necessary, to get culture report and bacterial sensitivity test. Since many antibiotic and chemotherapeutic agents are available now it is important to make the proper selection with regard to the immediate therapy and the ultimate control of the infection. One should then administer the proper dosage of the agent for a sufficient length of time to control the systemic manifestations of the infection and the fever, and then continue it for another forty-eight hours. This type of therapy alone might apply in an acute infection. Now where we have the patient in the chronic stage of pulmonary infection, the anatomic derangements are more than just simply inflammation of the bronchi. We have a complicated picture of destruction of pulmonary parenchyma and emphysema accompanied by fibrosis and

probably bronchiectasis. With the distortion of the bronchial tree and parenchyma, the ability to control infection is lessened and the need to get rid of the thick, purulent, or mucopurulent expectoration is even greater. The use of antibiotics alone in these instances is generally not sufficient. In the subsequent discussions I am sure the other aids that may be invoked will be mentioned; among these are the mechanical aids to coughing, instructing the patient in coughing, positive and negative pressure respirators, the use of enzymes, detergents and steam to help liquefy the sputum, bronchodilators and aerosolized antibiotics. The indications and contraindications for, and efficacy of some, are doubtful.

The prophylaxis of repeated infection is a complicated problem. It is not as simple from an experimental or clinical investigation point of view as, for example, the problem of evaluating the prevention of rheumatic fever by antibiotics. Here I feel we have a much more complicated situation and are not able with our present knowledge to make broad generalizations about the value of prophylactic therapy. I think we have to be guided by our knowledge of the course of each patient. In the presence of any clinical suggestion of a recurrence of infection, such as change in character or quantity of sputum, increasing shortness of breath, even in the absence of fever, one should quickly institute proper antibiotic therapy or chemotherapy.

Certain complications of antibiotic therapy and chemotherapy of chronic pulmonary infections which might be discussed later if time permits, are the emergence of resistant strains of bacteria and the reports of the development of pathogenic properties in some bacteria, yeasts and molds, which are commonly saprophytic. The relevance of these reported mutations is doubted by many competent bacteriologists.

MODERATOR RICHARDS: Thank you very much, Dr. Galdston!

Are there any comments from other members of the panel? Again we will come back to some of these questions later. We have been fairly free from controversy thus far but I think now we run head on into some problems that will provide differences of opinion and probably situations where the answers are not wholly forthcoming at the present.

These physiological data at the bottom of the first page I will pass over because we will come back to them later. Now we find that the man has a further clinical study, that the bulla in the right upper lobe is larger and seems to have caused mediastinal displacement. There is some right ventricular hypertrophy with the conus prominent. Bulla explored

by needle, air removed without improvement. The question of ganglionectomy was considered but not approved. He had the usual therapy, antibiotics and other physiologic therapy to which we will come back. After that, when he was better, an operation was performed and his right upper lobe was removed. He had a difficult time but thereafter was better.

This raises obviously a number of questions on what can be done surgically, what should or should not be done. I will ask Dr. Berry if he will comment on this particular series of events and on these considerations in general.

DR. FRANK B. BERRY: Obviously this is not a particularly favorable patient for surgery. In fact, the more extensive the infection throughout, the less favorable the person becomes for surgery. We have had no experience ourselves with ganglionectomy although I know Dr. Blades over the past few years became at first hopeful with the removal of the sympathetic, the vagus nerve from below, the recurrent, and then stripping the pulmonary artery, much as in Leriche's operation but his results were so poor and uncertain that he has given those up. We have had similar experience with some rather far advanced cases from moderately young people, in their twenties, thirties to a man of 65. During the last four or five months due to the kindness of Dr. Barach–I don't know whether to say kindness or not–I have had some interesting experiences with four of these very advanced cases and we did not quite know how to approach them at first. I might say that the two younger people have had little or no relief. Little was done to them. We did not much more than put in a needle. In one we inserted a catheter for a short time, more or less in the manner of Head, and let the bulla collapse around it. In the other two, we did a frank open operation and, since they were of some interest, they might be described briefly. The lung of one man in his middle thirties looked like a stick of balloons such as you see on sale at a football game. Realizing that any radical measures we might take would do more harm than good, we merely excised the top of one and sewed a tube into it so as not to disturb his lung cavity. It must be realized that in any of these people, the minute a part of the lung is removed and nothing more is done, the rest of the lung must expand to fill that space and if you are dealing with an already emphysematous lung, you increase the emphysema in the remaining lung. So it is all very well to take out a cystic area of the lung but if that is all that is done, perhaps

more harm than good results.

The fourth patient that I speak of was really a very extraordinary person. He was 65 years old. Nobody wanted to operate on him but he apparently had a very large bulla in his right upper lobe and at operation his right upper lobe looked like a very large inflated balloon, perfectly motionless and we had to stop. His middle and lower lobes were collapsed below it. We had to stop very frequently in doing that lobectomy but the minute that the lobe was removed his condition improved. We then came to the realization that he would not stand a decrease in the size of his chest, at least on that day, and that if we did not do something that day he would probably not survive because the rest of his lung could not take over. It was already emphysematous and would be in a worse condition, and in order to meet a bad situation we stripped the pleura from his ribs and placed a large plastic sponge outside of it so that we did not increase his space. We decreased his space and allowed his middle and lower lobes to function at their maximum capacity. It seems to me that quite by accident we stumbled upon a possible help in such instances, because for the past four months that man has been in infinitely better condition than he was. He did not have a stormy convalescence. Instead of living in oxygen, as he had been continually for six months, he was out of it in four days. So if surgery is attempted on these people at all it seems to me that great care should be exercised to maintain or to decrease the space after that portion of the lung is removed, so as not to increase the strain,—in other words, not to make the disease worse. Certainly these patients are entirely different from the young patients with solitary cysts or giant bullae with the remainder of the lung in good condition.

MODERATOR RICHARDS: This discussion obviously raises some very interesting general problems. *I am going to ask Dr. Comroe and Dr. Cournand a few questions to bring this out further, perhaps first Dr. Cournand, on this problem of space filling in chronic pulmonary disease generally and the problem as it is encountered particularly in emphysema such as we have here.*

DR. ANDRE COURNAND: I might state at first that all that I know about the behavior of cysts in patients with emphysema I have learned from Dr. Berry, so for once the physician will agree with the surgeon.

DR. BERRY: Thank you!

DR. COURNAND: At first it was not unusual to see a large bulla develop

as the lung expanded after a solitary cyst in one lung had been removed from an emphysematous patient. So I think it is extraordinarily important either not to operate on such cases or, as Dr. Berry suggested, to reduce at the same time, permanently or temporarily, the size of the lobe which remains, or that portion of the lung which remains. I think that this problem is one which should be considered seriously in this particular case because with the degree of emphysema indicated by the figures in the protocol, the constantly decreasing respiratory volume, we are dealing with a generalized emphysema. If you collapse one lung, you are returning to a type of treatment which was suggested many years ago, I believe in Austria, to do a pneumothorax for the treatment of emphysema, that is, reduce the distention of the emphysematous lung. I think that should not be done by physicians because it may lead to disaster, and, of course, it is not so different from the treatment which has been proposed recently of introducing gas under the diaphragm, lifting, helping the diaphragm to raise and reducing the distention of the lung which in some hands gives good results. In our hands it has not resulted in improvement of the patient.

I think that one might investigate what Dr. Berry has suggested, of trying to maintain the space smaller than it actually is by mechanical means, with caution and care. I believe in his hands it might be good. In other hands it might not be so good.

MODERATOR RICHARDS: *Dr. Comroe, would you continue the discussion in any way that you would like, either this problem of space replacement by mechanical means such as Dr. Berry suggested, or comments on pneumoperitoneum, which Dr. Cournand has mentioned, or any other aspect of this situation?*

DR. COMROE: What I would have to say would simply be on theoretical grounds and that is, that I do not believe that distention of a lung per se does any harm so far as gas exchange is concerned. In other words, if I am breathing, as I am right now, I have good gas exchange and if I also inflate my lung to near the maximal position and continue to ventilate there I also have good gas exchange. It is not the size of a lung that is important. It is whether there is good ventilation of the lung that has good blood flow through it, so that I have never been completely convinced that over-expansion of healthy lung does very much harm, any more than taking a deep breath does. Now I may be completely wrong on that. I think that in order to get good evidence on that point, one

would have to follow patients with lobectomy or pneumonectomy for a very long period of time and see what actually happened to them.

So far as the matter of compression of lung tissue is concerned, whether the lung is compressed from within the thoracic cavity by some foreign material or whether the lung is compressed by raising the diaphragm, by pneumoperitoneum, again I am wondering what the compression compresses because from what we know about healthy lung tissue we know that it is easier to collapse healthy lung tissue that has good elastic recoil than it is to compress emphysematous lung tissue that does not have elastic recoil. In studies that have been done in Professor Christie's laboratory in London, they have actually observed the lungs in a plastic thoracic cage after autopsy and have found on inflation of the lungs the bullae fill very nicely but when the time comes for deflation the healthy lung deflates first and it requires a pressure on the positive side in order to get any air out of the emphysematous bullae—so that I am not completely convinced about this matter that you can compress a lung by one manner or another and help that individual by this mechanism. I think, however, if you do something to the lung which improves the ventilation of the emphysematous area, not its volume but its ventilation, then you may do some good. Raising the diaphragm, of course, may make the diaphragm more efficient and may make a better bellows of it.

MODERATOR RICHARDS: *Do you want to comment further, Dr. Cournand?*

DR. COURNAND: I agree partly with what Dr. Comroe has said, that obviously, when you collapse an emphysematous lung, you collapse first the good alveoli. We showed that about 20 years ago with Dr. Richards in well documented cases. I think what Dr. Berry suggested is not so much to collapse but to prevent overdistention and we also have evidence, from a study of pneumonectomy in patients who have had bilateral emphysema, that overdistention of the emphysematous lung is not very favorable physiologically. There is also no doubt that in the patient with emphysema what you collapse first by pneumothorax is the normal alveoli. For that reason I think pneumothorax should never be proposed for the treatment of emphysema.

MODERATOR RICHARDS: On this question of pneumoperitoneum, or in fact of any type of pressure on the abdomen with the intent to raise the diaphragm, I think Dr. Christie's observations, as Dr. Comroe pointed

out, are significant and may be quite important in explaining the lack of improvement that one so often encounters. It seems as though the use of moderate pressure upon the abdomen simply by the hand, following the patient under the fluoroscope or even better, also measuring his vital capacity, can sometimes indicate very quickly whether that type of procedure will be effectual in improving performance or not. This, of course, applies to any type of pressure raising the diaphragm, perhaps more to the use of belts rather than the use of gas in the abdomen which has many more problems connected with it, as you all know.

If there is no further discussion on this point, we can proceed through this patient's course and then address ourselves to therapy as the condition moves on to cor pulmonale, as well as pulmonary insufficiency as such.

Well, in 1952 then, he had another cold, with fever and cough and he had gone on a reduced ambulatory regimen, had the usual trouble following this cold and he then proceeded to develop right-sided congestive failure, cor pulmonale, was in failure, with progressive swelling of his legs, cyanosis, dyspnea, cough. He had thick sputum, fever, rapid pulse, respiration was gasping. He was very badly off indeed with this particular episode. Asthma, emphysema, combined with the thick sputum completely asphyxiated him or very nearly so and he could hardly breathe at all. It is found now that his heart was enlarged, had a gallop rhythm, dullness and rales at both lung bases, wheezing. He had polycythemia. He was given actual mechanical suction, which brought him out of his desperate state and he was then found to have a very low arterial blood oxygen saturation and a very high carbon dioxide in his blood. We might go back to the protocol to see what his situation was prior to this severe episode. One finds that he had a maximum breathing capacity, the maximum amount that he could breathe into and out of the spirometer, down to 25 liters a minute compared with the normal of about 90. The amount of residual air in his lungs—the residual air, as you know is the amount left in the chest, in the lungs at the end of a maximal expiration,—and which is normally about 30 per cent of the total lung capacity, the total volume at the height of inspiration—was now up to 60 per cent. On complete expiration therefore he still had 60 per cent of the total capacity of his lungs filled with residual air. He had a moderately reduced arterial-oxygen saturation, a moderately increased CO_2 level in his blood and the tension or pressure in the blood corres-

ponding, and of course the venous plasma CO_2 was also increased.

Let us go back then to the situation where we just left it. He deteriorated so that the arterial saturation was down to 62 per cent, the arterial CO_2 further increased and he was placed in an oxygen tent. He improved for a short time and then rather rapidly went into coma. His arterial oxygen saturation was found to have been raised to nearly normal and the arterial CO_2 went up very high indeed. He was taken out of oxygen, given a mask respirator which did not work, replaced with a Drinker and that did improve him measurably. He was able to be removed from the Drinker after ten days. He then had vigorous therapy, digitalization, mercurials, repeated phlebotomy as well as bronchodilators, etc. He was able to be about. He had some improvement in his blood values as you see, was able to be sent home on bed-chair regimen with the same medications, using a respirator intermittently during the day. He rocked along fairly well for a short time and then one morning was found dead in bed.

Here are a lot of things to consider and I think perhaps we may first take up the general treatment of cor pulmonale as a whole clinical entity, both the pulmonary and cardiac aspects and this particular problem of CO_2 narcosis will be given special consideration.

I will ask Dr. Cournand, if he will outline for us very briefly what the principles of treatment in this severe situation are.

DR. COURNAND: It is essential to state first that the treatment that I shall outline is the treatment in a patient with chronic pulmonary emphysema. I shall not speak about the treatment of cor pulmonale in patients with severe fibrosis where the pathology is quite distinct from that of the chronic pulmonary emphysema. If we have time, we might say a few words about it.

In pulmonary emphysema, the failure of the heart is preceded by a period during which anoxia has a deleterious effect on the circulation in several ways: first, chronic anoxia tends to increase the heart rate, possibly has some effect upon the metabolism of the heart and as a rule, per se, tends to increase the output. On the other hand, chronic anoxia will tend to stimulate the bone marrow and increase the amount of blood circulating with the ultimate result of an increased mass of blood in the lungs and in the general circulation. Anoxia also has a definite effect upon the pressures of the pulmonary artery and since the blood volume in the pulmonary vessel is already increased and there is a definite effect

upon the smaller vessels which tend to increase the resistance to flow, the pulmonary arterial pressure is going up. Therefore you have a situation where, with a pulmonary vascular bed which is somewhat reduced in size as the result of the emphysema, increased pulmonary resistance and increased output tend to raise the pressures and obviously increase the work of the heart. If there is an acute episode of anoxia, a large number of red blood cells are rapidly thrown into the circulation, there is an increase of mass volume and, with the increase of anoxia the heart, which had previously hypertrophied, will dilate further, and will fail. I think that the treatment which we will outline is a logical one and one which in our hands has given quite satisfactory results. Of course, the heart is failing and so one gives digitalis. I am not absolutely sure that you could not bring these patients back to normal function without giving digitalis. One does not dare to do that. The second thing is, of course, to eliminate anoxia and in order to eliminate anoxia which has several bad effects,—increased pressure in the pulmonary artery and circulation, increase of volume of blood,—you have to open up the airways. That means eliminate the spasm in the airways, possibly decrease the mucous membrane edema by the use of bronchodilator drugs. Then you have to use antibiotics in order to eliminate the secretion, which is sometimes tenacious in the airways and by restoration of a better circulation of gas through the airways remedy the oxygen situation,—I am not speaking about the use of oxygen. I will leave that to Dr. Comroe. I would probably agree with him that if you use oxygen in such a case, then you must hyperventilate your subject. Since the blood volume is greatly increased the logical thing is to remove blood and you can do phlebotomies and you can do repeated phlebotomies. Don't phlebotomize too large quantities at one time but you can repeat it. This is the treatment of cor pulmonale in the acute stage. You have not finished treating your patient because you have to follow him and to prevent, if at all possible, the recurrence of the acute episode of anoxia hypervolemia and polycythemia.

Just in so far as the first one is concerned, you must, of course, treat the patient with bronchodilators and antibiotics. We indicated you may possibly use mechanical ventilation to improve the situation. You must also maintain the blood volume at a lower level and by following the hematocrit regularly you can determine the time when phlebotomy will be helpful. As a rule we try to maintain the hematocrit of this indi-

vidual at between forty-five and fifty, not beyond that. Of course, during the entire period of time in the acute stage of cor pulmonale, and in the period which follows after the patient has been improved, it happens that as a rule the patient still has a very high CO_2 tension and a very high alkaline reserve. A number of efforts have been directed against this deleterious effect of the high alkaline reserve with the high CO_2 tension. I don't know whether this is the time to discuss that or discuss that after Dr. Comroe has spoken about the treatment of anoxia.

I should like to mention in passing that recently we have treated a fairly large number of patients with chronic pulmonary emphysema who had been once in failure, had been actually improved by the acute treatment that I mentioned, and in whom we brought down the alkaline reserve by using a carbonic anhydrase inhibitor, Diamox, with what I would call fairly satisfactory results.

MODERATOR RICHARDS: I have a fervent plea from one member of the audience to be specific in our therapeutic approach. We will follow that suggestion and try to take advantage of it.

DR. COURNAND: May I ask the person who made the plea whether I was specific enough?

MODERATOR RICHARDS: If not, we will perhaps have further questions asking for actual dosages. I should think in terms of principles, Dr. Cournand, you were very clear. We may get to specific dosages and regimens presently. As Dr. Cournand implied, the question of CO_2 and the question of oxygen are all bound in together and the question of oxygen therapy moves into the question of the management of, the elimination of CO_2. With our new devices, mechanical and otherwise, we can do rather better on some of these problems than we used to do.

I will ask Dr. Comroe, if he would like to discuss this problem from any angle he wishes, but especially the therapeutic approach.

DR. COMROE: The problem that I am going to discuss is simply this, patients who have chronic anoxemia and CO_2 retention resulting from pulmonary disease, chronic in type, may come into the hospital, be given oxygen therapy and shortly thereafter may go into coma. This has been written about by Dr. Barach, Dr. Cournand and Dr. Richards. We first noted this sequence after they had brought it to our attention. A patient walked into the University Hospital in Philadelphia not in very good health, but he was ambulatory, he was cyanotic, and he did have chronic emphysema. The intern put him in an oxygen tent or, I believe, gave

him an oxygen mask, and in two hours he was in coma and he never recovered from the coma. We subsequently studied a large series of individuals to see how frequently this occurred and I am glad to say that it does not occur very frequently.

I would like to say first of all that you must not withhold oxygen therapy from a patient who might be benefited by it, because of fear of putting a patient into coma. We have seen a patient who had very marked ankle edema, in fact the edema extended all the way up the thighs and people were very much puzzled about this, because there was no other positive evidence of disease in this individual except for this edema. The patient was sent up to us not because anyone thought the patient had chronic pulmonary disease but because I had talked in a seminar that day and they did not know what else to do with the patient. We had pulmonary function studies done. The patient was anoxic. In fact, he had marked CO_2 retention. The patient was given oxygen, did not go into coma and in two days the edema was gone. I would like to emphasize that oxygen therapy should be tried. However, whenever you give oxygen therapy to a patient with chronic pulmonary disease and pulmonary insufficiency you must realize that possibly one out of ten, or one out of eight, of these patients may become somnolent or may have mental irritability, signs of central nervous system irritability, and if you want me to be specific, I would say—try oxygen therapy in these people with chronic anoxemia. I would watch them closely for several hours in order to see whether there was somnolence. Sometimes somnolence means a patient has been dyspneic for a long period of time and has not been sleeping well. You reduce the minute volume of breathing, and the individual falls off to sleep. If the patient shows more than this somnolence you must do what Dr. Cournand says, do some hyperventilating along with giving of the oxygen. This phenomenon in which the patient is given oxygen, becomes nice and pink and goes into coma has been called CO_2 narcosis. There is no doubt that an increase in CO_2 pressure in the blood, if high enough, will cause narcosis. Indeed 30 per cent CO_2 has been used for surgical anesthesia. I think that most everyone is convinced that this is a state of CO_2 narcosis—the patient has been anoxemic, the anoxemia has been driving the breathing and on suddenly giving oxygen, you oxygenate while cutting off the CO_2 and the drive to respiration is depressed, and when depressed CO_2 builds up. However, there may be other factors involved such as the removal of

the anoxemic stimulus to the cerebral cortex or certain metabolic changes but I don't think we will go into those today.

In trying to figure out what to do for an individual who has been given oxygen and goes into coma, you will say he needs oxygen. You don't want him in coma so you try to hyperventilate him, give him good ventilation, oxygenate the blood fairly well and also get rid of the CO_2. How are you going to go about this? You can try some of the various mechanical devices, the body respirator,–the Drinker is one. Positive pressure breathing by applying a mask to the nose and mouth and inflating the lungs that way is another, but I want to give you a few words of caution about these mechanical aids. I think Americans have great faith in apparatus and machinery. As long as a person is hooked up to a piece of machinery they think everything is being done that can be done. We have had two people in the Drinker respirator this week. One of these, with the Drinker respirator going maximal depth and maximal force of inspiration, was not being ventilated sufficiently. This was simply because this particular patient had changes in his lungs which made his lungs stiffer and more rigid. However, it is generally believed that if you put a person in the Drinker and set it at full force, he is going to be hyperventilated. This is not necessarily true. I believe that every Drinker respirator or body respirator ought to have a device for measuring ventilation, not the force supplied to the thorax but how much air is going in and out the individual's nose and mouth. We usually do that just by putting a mask over it to the BMR machine to see what is the tidal volume. You can do it in other ways by following CO_2 and seeing whether the CO_2 comes down. If it is coming down you are hyperventilating. If it is not, you are not!

There is another thing to remember about the Drinker respirator in this connection–these patients are usually unconscious. They are in coma. You must be very careful to manage these patients exactly as though they were unconscious patients after operation. You must prevent secretions from going down into the respiratory tract. You must prevent anything regurgitated from the stomach from going down the respiratory tract. The position of the patient in the Drinker respirator is a very bad position for the patient because he is in the supine position. It would be very nice if there were sitting Drinker respirators, instead of supine, horizontal ones. Since there are none at the moment, the thing that I particularly want to emphasize to you is that when you try to hyper-

ventilate a patient by whatever method you select, make sure that you are accomplishing your aim.

The first man I mentioned who was in the Drinker respirator was not being hyperventilated because his lungs are stiff. The second patient is being hyperventilated, we hope for a different reason. His lungs are not stiff. However, while he is in the Drinker respirator we measure his tidal volume and find that for about four breaths he may be breathing 800 or 900 cc. which is very good, and the next three breaths he may be breathing 50 cc., and the next four or five 200, and the next 800, and the next 500 to 600. That indicates to you another complication of the Drinker respirator and that is, that patients will tend to "buck" the respirator. If the patient is breathing 16 times per minute and you can get the Drinker to breathe 16 per minute, you will probably accomplish hyperventilation, but if the patient wants to breathe at 22 and you have the Drinker set at 16, the patient may be breathing in while the Drinker is pushing out and the ventilation accomplished is less than it would be if he were on his own without the Drinker. I do not mean to say you should not use the mechanical aids. You should use them with the knowledge that you may not always be accomplishing what you want unless you actually stand by and see that you improve the ventilation. I think that is the most important thing I want to say about that aspect of it.

MODERATOR RICHARDS: *Are there any comments from among the members of the panel?*

DR. GALDSTON: Would you comment about the other types of mechanical aids that would be available, say at home or not in the hospital?

DR. COMROE: I find a lot of individuals are purchasing their own positive pressure devices. One of these is the intermittent positive pressure device which operates through a mask and applies a positive pressure to the airway and then with expiration the gas comes out again. One of these is called the Neoventilator, another called the Bennett valve, which patients are purchasing and using at home with the idea of increasing their ventilation. We have a patient at present who has bought one of the intermittent positive pressure devices and is using that pretty frequently. I think that he is using it because of the fact that his lungs are pretty stiff and it costs him a great deal by way of muscular effort and energy to inflate his lungs, so he inflates his lungs with a machine and lets the chest and lungs recoil pushing it out. I think that that is probably a fairly valid use of the instrument. He has devised a way of using it

I have never seen before and that is, he lets this thing fill him up on inspiration and then pulls it out of his mouth so that he does not have to force out against any positive pressure. So he has developed a sort of intermittent valve of his own in putting it in and taking it out, but generally the machine will do that.

The cuirass respirator, which is something which, as a rule, fits over the chest alone is not so efficient as a body respirator simply because of the fact that when you enlarge the thorax you may do two things. You may pull air into the lungs and you may pull the diaphragm up and the abdomen in, whereas in the big body respirator which encloses the whole body below the neck, you are pulling the diaphragm down and enlarging the thorax simultaneously. I think the cuirass is useful sometimes but certainly not as powerful an instrument as the body box may be.

MODERATOR RICHARDS: *I have a series of questions directed to Dr. Sherman as to the use of ACTH or cortisone, noting that it was not employed in this case and asking for guidance about its use for or against, in either asthma or more particularly this type of chronic disease.*

DR. SHERMAN: I was very much surprised in reading over the protocol to see a patient who had so much treatment of so many different kinds who had not received either ACTH or cortisone. I do think a trial of one or both of these agents was certainly warranted. At the stage where he was started on desensitization injections in 1947 or 1948 the drugs were not available. Then perhaps in 1951 when he was still not completely in a state of irreversible emphysema they might have been tried.

In discussing the use of vaccine therapy in the management of the chronic infective asthmatic patients I mentioned that this was not very satisfactory, far less satisfactory than the handling of asthma due entirely to extrinsic allergies. In this type of case there has been an increasing tendency to use ACTH and cortisone,—ACTH usually during the acute flare-ups for temporary relief and cortisone over a period of time to control the asthma in a patient who cannot be adequately controlled by other measures. I feel that during the time when this patient was suffering primarily from asthma without too much irreversible change in his lungs that a great deal might have been accomplished if he were carried over a long period of time on a small maintenance dose of cortisone, the dose being regulated to the smallest amount which would satisfactorily

control his symptoms. Usually that is somewhere in the vicinity of 25 mg. twice a day. With this type of dosage many patients can be continued on the treatment for months or even years without developing any of the adverse side effects because the dose is very small. Some patients will be greatly relieved by it and it may make more difference in controlling their asthma than all other measures combined. Therefore, I think it is a very worth while treatment. It is a worth while treatment but it is one that we have tended to use as a last resort in cases where the older methods have not been successful. However, when necessary it is useful. The side effects with the doses of that size are far less than one might imagine and incidentally, in recent years the cost has become relatively small compared to the amount of disability that may be saved.

DR. COMROE: Is there any problem in using cortisone in these patients who may have a fair amount of pulmonary infection?

DR. SHERMAN: Yes, there certainly is. I was thinking more in terms of the stage before he was having fever and having a great deal of purulent sputum. I believe that the cortisone is most effective when the patient is reacting in what we consider the reaction of bacterial allergy where there is a relatively small amount of infection but an excessive reaction to it. In any such instance it is, of course, important to follow the patient closely and at the first sign of any acute infection to institute antibiotic therapy. In some cases small doses of penicillin, so-called prophylactic doses, or Gantrisin have been given over a period of months in an attempt to prevent flare-ups of infection. However, the prevention is not too satisfactory and it is more a question of vigilance, to treat it vigorously when it does occur.

DR. COURNAND: I would like to ask Dr. Sherman whether he believes that this patient in 1945 had asthma and developed emphysema as the result of his asthma or whether the asthmatic bronchitis that he had was not a manifestation of his chronic pulmonary emphysema and therefore ACTH was then not indicated as a treatment?

DR. SHERMAN: From the amount of material in the protocol, I think it is very difficult to say. I would say that in 1946 when he had a severe attack of asthma lasting three days, my interpretation of this severe attack would be that at the time he certainly was really having asthma and it was not simply an asthmatic manifestation of emphysema. However, I think we would have had to see the patient at the time to really make a definite distinction.

DR. COURNAND: He already had bullae on the x-rays so he had emphysema. We will underline that. I think it is very important because it brings up the question whether the asthma in patients who have proven chronic emphysema has been a factor in the development of emphysema or whether the asthma is misnamed and is not strictly asthmatic bronchitis. In my experience this is the more common occurrence. I am not an allergist of course.

DR. SHERMAN: I would certainly agree with Dr. Cournand and it is difficult to say. Even after following the patient over a period of time it may be rather difficult to say dogmatically. I would say that back in the stage of 1945 it would be very interesting to know whether his sputum and perhaps his blood showed an increase in eosinophils, whether there were other evidences of actual allergy at that time, but from the information in the protocol, I think that one is entitled to either opinion, and there is no way to decide definitely.

DR. COMROE: This case report says "1945,—attack of virus pneumonia with slow recovery." We have seen several people with well advanced pulmonary insufficiency in whom it was impossible to get any history of anything which might be leading to emphysema, in other words, no asthma, no chronic bronchitis, no sputum, no cough and yet they had the history of having had an attack of pneumonia three or four months previously which incapacitated them for several weeks. There was slow recovery.

When I was in medical school, long before chemotherapy was in vogue, we used to be taught that one either died or recovered completely from pneumonia. I am not sure that that is true of some of these so-called virus pneumonias, the ones that don't respond to chemotherapy and I am wondering whether some of these don't lead to permanent lung damage, which we see a few months or a few years later as emphysema.

DR. GALDSTON: It might be pertinent to remark here that in the first paragraph this man is said to have had a cigarette cough for twenty years, with mucoid expectoration. It is conceivable that he has had a longstanding bronchitis due to physical irritation associated with his so-called cigarette cough, and whether it is directly related to smoking cigarettes or not we don't know. But the fact is that he has had a moderate degree of bronchorrhea over a period of twenty years, coming up to the age of 59 or so, where he might be subject to additional changes with age in the pulmonary elasticity. He now has in addition, another

possible cause for perhaps irreversible changes as the result of the so-called virus pneumonia. I think that these are all important points that come up in his history.

DR. COURNAND: Maybe he had emphysema for twenty years.

DR. GALDSTON: He may have had it.

DR. COMROE: That is a good point because all of us as we get older get some pulmonary changes. Dr. Galdston has noted this, as we have. Individuals in the older age group whom we think perfectly normal, may have some changes in the lungs that are detected by pulmonary function studies. So a man who has a certain amount of pulmonary disease which does not incapacitate him, when he gets to a certain age this amount may incapacitate him simply as a result of the aging process.

DR. GALDSTON: Maybe he is using up some of the reserve at a faster rate once the infection comes in.

MODERATOR RICHARDS: *This is not in the program as announced but I believe Dr. Barach is here. I wonder if he would like to make any comments either on the use of respirators or anything else in the discussion thus far. We have a chair up here and a lapel microphone if he would like to to use either one or both.*

DR. BARACH: Thank you very much!

The only comment I would like to make is about the last statement of Dr. Comroe. He mentioned a virus atypical pneumonia preceding a bad emphysema. I have seen about twenty people in perfectly good health, some of them almost in the athlete class, who, four or five months after atypical pneumonia, developed full blown pulmonary emphysema. I don't remember ever having seen it after a bacterial pneumococcus pneumonia but I do believe that so-called atypical pneumonia in a middle aged group should probably be treated with excellent care because during the period of coughing that often takes place in this disease the bronchi appear to be and the parenchyma of the lungs appears to be in such a weakened state that organic emphysema does take place afterwards.

MODERATOR RICHARDS: It really illustrates how little we know about the genesis of emphysema. This apparently is one, I am sure it is not all, of the factors that lead to emphysema. Fibrosis may not exist at all in emphysema; but the essential process may be as much atrophy as fibrous tissue change.

How all this comes about we are still rather much in the dark. Are there any further comments? If not, I wish to thank the members of the panel very much.

DIAGNOSIS AND TREATMENT OF MENSTRUAL IRREGULARITIES*

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THE phrase "Menstrual Irregularity" is an extremely loose one and can have many definitions. To one person, it is too little, to another too much bleeding. To another it means that the menses are too early or too late and so on. One patient considers excessive flow as normal and another considers normal flow excessive. To begin with then, confusion comes to this subject quite naturally. I shall limit my discussion chiefly to patients that bleed too much and to those that don't bleed at all.

An adequate scientific approach to the problem is still lacking. We have approached the problem from a theoretical point of view, one which we believe to be quite practical. We see demonstrated here (Fig. 1) in a diagrammatic fashion the estrogen and progesterone levels of a normal ovarian cycle. An attempt is made also to show the relative size of the endometrial mass. In the lowest portion of the slide is seen a typical biphasic temperature curve which comes in a normal ovarian cycle, following ovulation. This yardstick of a theoretically normal ovarian cycle is placed alongside the patient's irregularities. An attempt is made to determine the patient's deficiencies.

We have an Ovarian Dysfunction Clinic at the New York Hospital where patients with menstrual irregularities are accepted for clinical study. This clinic has been in existence for approximately eight years. In the beginning only patients with secondary amenorrhea were accepted and repeated attempts were made to produce ovulation in these patients. As the clinic has been longer in existence other types of irregularities have been accepted. At the present time the patients fall chiefly into two large groups, those with secondary amenorrhea and those with so called "functional bleeding." It has seemed to us that the underlying problem in these two groups of patients is very similar. It is merely a

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TABLE I—SECONDARY AMENORRHEA METABOLIC PROBLEMS

1. Weight gain
2. Thyroid hypofunction
3. Weight loss
4. Possible thyroid hypofunction

matter of degree which differentiates them. Ovulation is the cure for either group, therefore, most of our efforts have been directed towards trying to make them ovulate, in fact, a better term for the clinic might be "Ovulation or Attempted Ovulation Clinic."

I am not going to quote you a mass of statistics which would be of no real value, but on the other hand I would like to tell you some of the experiences we have had in trying to make these patients ovulate. The first group to be discussed will be those patients with secondary amenorrhea (Table I). In our group of cases excessive weight gain has been the chief offender in causing people to stop ovulating. Why this is true I cannot tell you, but suffice it to say, as you all well know, that if the obese patient with amenorrhea can lose a sufficient amount of weight she will frequently begin to ovulate and menstruate again. The amount of weight gain which causes this to occur varies with the patient. There are some patients who need only to gain ten to fifteen pounds in weight before ovulation will cease and at times anovulatory bleeding as well. An equally common cause of failure to ovulate has been thyroid hypofunction. It is often found alone or at times in conjunction with excessive weight gains. This finding can usually be determined by laboratory studies and replacement of thyroid brings about prompt resumption of ovulation and menstruation. Weight loss is rarely the cause of failure to ovulate. It may be influential when the weight loss has been a very great one, or when the patient has lost weight rapidly and carried the process of reduction to extremes. I might add that to get one of these patients to gain weight again is sometimes more difficult even than trying to get the obese patient to lose. I have noted here a fourth heading under the secondary amenorrhea in the presence of metabolic problems—possible thyroid hypofunction. Even when all known tests prove the thyroid to be functioning normally there still are a few of the patients who will return to normal ovulation following the use of thyroid. Just why this

TABLE II—TREATMENT OF AMENORRHEA
NORMAL METABOLIC FUNCTION

1. Cyclical Progesterone (Coincidental ovulation)
2. Cyclical Estogren-Progesterone
3. X-ray stimulation

seems to be true I cannot state. Some endocrine clinics in this country advocate the use of thyroid to clinical tolerance without any reference to known thyroid studies, namely B.M.R., blood cholesterol and protein bound iodine determinations. To summarize this group one might again say the first thing to do with the patient in secondary amenorrhea is to correct metabolic problems.

If metabolic functions are considered to be normal or have been returned to normal by the procedures outlined above the next step to take is the addition of progesterone in a cyclical fashion (Table II). We advocate the use of a rather large dose of progesterone. At the present time we are using the sublingual form, about 60 mg. daily for three to four days. This is only about one-fifth of the amount of progesterone which the normal corpus luteum is thought to secrete in its period of activity. If the use of progesterone is followed by withdrawal bleeding of an adequate nature it is our interpretation that the patient is making some estrogen and perhaps enough. If this dosage of progesterone is not followed by withdrawal bleeding then the patient must have estrogen and progesterone in a cyclical fashion. It is our feeling that the smallest dose of estrogen which can possibly be used is the better. This will prevent any inhibitory activity upon the pituitary. It is generally accepted that there is no good gonadotropic hormone available. The cyclical use of progesterone or estrogen and progesterone is the best method known by which steroids may be used to set the mechanism of ovulation and menstruation back to work. In some patients we have noted that a coincidental ovulation occurs soon after progesterone is given the patient. This can be noted by the persistent rise in the temperature chart which ends in menstruation fourteen days after the onset of the temperature rise. I am not speaking now of the slight hyperpyrexia which some patients get from the use of progesterone but rather of a true ovulation which occurs shortly after the

TABLE III—SECONDARY AMENORRHEA OTHER CAUSES

1. End Organ failure
2. Stein-Leventhal syndrome
3. Other abnormal states
4. Abnormal emotional patterns

progesterone is started. This group of patients of course is the most favorable of any and many of these have been able to conceive and produce living infants. When there has been failure to effect ovulation after twelve to twenty-four months of the cyclical use of estrogen and progesterone, x-ray stimulation is advised. It has, however, not been used if the urinary gonadotropin assay is abnormally high. Many workers have shown x-ray stimulation of the ovary may end in ovulation. I certainly have no hesitancy in suggesting that a patient receive x-ray stimulation of the ovaries when she has had a sufficiently long period of unsuccessful substitution therapy from estrogen and progesterone. Many patients have been hesitant about the use of x-ray and have decided that they would not go to that degree of abnormal stimulation in the hopes of ovulation and conception.

In cases of secondary amenorrhea from other causes (Table III), end organ failure does occur although it is very frequently hard to prove. In a series of fifty cases previously reported five of them were found to be due to end organ failure. All five of these occurred as a result of curettage following abortion or the removal of secundines, some two to four weeks following delivery. About twelve to fifteen patients have been studied with a diagnosis of Stein-Leventhal syndrome. All these patients have been operated and a wedge resection of the ovaries carried out. Two of the patients have delivered term babies, and one is pregnant at the present time. The greatest success has been had in those patients in whom there has been an adequate elaboration of estrogenic hormone. Here is a place where the daily vaginal smear is of value. We have been guilty of using this test too infrequently in our studies. Patients who have failed to ovulate following operation for Stein-Leventhal syndrome and other adrenal states have been tried on cortisone therapy. The greatest success in this group has been found in the overt adreno-genital cases where there was very definite labora-

tory evidence of adrenal hyperplasia. Some of these patients have conceived but none of them have as yet gone to term.

Lastly, I have mentioned here, although it should by no means be in last place, abnormal emotional patterns. The longer one studies these patients with endocrine problems the more one becomes impressed with the effect of the psyche upon ovulation and menstruation. We have sought the aid of the psychiatrists, and have implored the Department to assign a man to our clinic. This has been as yet impossible. Some of the patients have been studied at length, though none of them to my knowledge have had complete psychoanalytical investigation.

The second group of patients to be discussed are those with abnormal or excessive bleeding. These patients have been examined in the gynecological clinic and no obvious cause for the abnormal bleeding has been found. A tentative diagnosis of functional bleeding has been made and the patients referred to us for further investigation. Most of the patients have had vaginal smears made for cancer detection before they reach our clinic. Patients with obvious organic lesions are not included. The patient with a single abnormal period or even two is likewise not included. We feel that an occasional irregularity can happen to almost any patient and one should not speak of functional bleeding until something more abnormal than one or two periods has been evidenced. We are particularly interested in the patient with menorrhagia or metrorrhagia where no cause for abnormal bleeding can be found on routine examination. The yardstick of a normal cycle is applied to these patients (Fig. 1). The patient is asked to keep a record of her awakening rectal temperatures and an endometrial biopsy is obtained just prior to or at onset of menstruation. If there is temperature curve evidence of ovulation and an advanced secretory pattern is found on biopsy we must conclude that the patient is having a normal ovarian cycle. Our theoretical statement is that a normal ovarian cycle ends in normal menstruation. Any patient then who bleeds abnormally in the presence of a normal cycle must have some organic cause, local or systemic. There are of course some exceptions to this rule but they are few. This diagnostic approach can safely be applied to any abnormal bleeding case. X-ray study of the uterine cavity, blood studies, careful examination under anesthesia, perhaps repeat curettage, everything must be employed to find the cause. Certainly there should be no place for hormone therapy in the presence of a normal ovarian cycle. Now, if there is no evidence

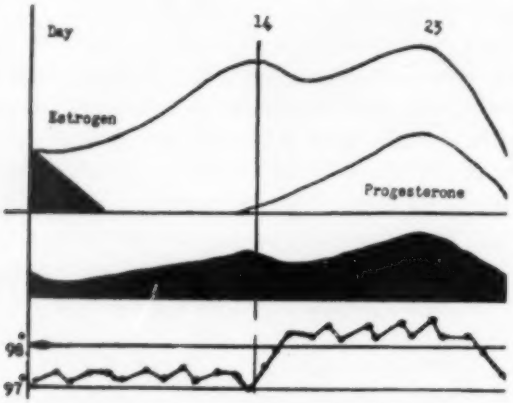

Figure 1—The normal ovarian cycle showing changes in hormone levels, size of the endometrial mass, and basal temperature.

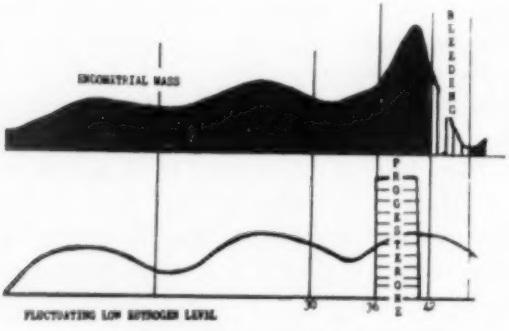

Figure 2—Effect of progesterone administration in a low level estrogen anovulatory cycle.

of ovulation then the patient receives a final diagnosis of functional bleeding and hormone therapy is instituted. The patient receives that hormone which she fails to make, namely progesterone.

In Figure 2 an attempt is made to demonstrate what happens when progesterone is given to that patient who is making estrogen in small amounts and gradually building up a larger and larger endometrial

TABLE IV—SECONDARY AMENORRHEA DOSAGE OF PROGESTERONE

Oral	100 mgm. daily x 5
Buccal	60 mgm. daily x 3½
I.M.	25-50 mgm. daily x 3-2

mass. Following the cessation of progesterone therapy and the subsequent quick disappearance of this hormone from the blood stream there is a complete shedding of the endometrial mass. The same thing happens when there is a high level of estrogen present. When the progesterone build up is removed a vascular crisis occurs which ends in normal and complete shedding of the endometrium. Progesterone can be given in any form, the cheapest is the buccal or sublingual tablet. The dosage will vary with the type of medication. Table IV shows suggested comparable dosages, oral, buccal and intramuscular. It seems impossible to give too much progesterone. In trial cases we have given large doses, 100 mg. intramuscular progesterone daily for ten days to see if abnormal bleeding could be created and to date this has not been possible. It is apparently the sudden withdrawal of this hormone that is important. Small dosages or gradual withdrawal of larger doses is ineffectual. The addition of progesterone in the fashion described is merely temporary treatment and the only true cure for the functional bleeder, as in the patient with secondary amenorrhea, is to effect ovulation. All metabolic problems must be corrected. Hypothyroid activity should be looked for.

A case history is presented for emphasis. Mrs. L. B., a twenty-nine year old married woman para 2, gravida 2, was admitted to the hospital in mild shock. Hbg. 4 grams. She was complaining of profuse vaginal bleeding for seven days. The patient had always had a normal menstrual cycle up until several months before admission, at which time the periods occurred forty days apart instead of her usual twenty-eight days and lasted nine to ten days with bleeding of hemorrhagic proportions. A dilatation and curettage showed hyperplasia of the endometrium. The patient was discharged and was seen again in seven weeks, bleeding profusely. An endometrial biopsy specimen was procured and the patient instructed to take 60 mg. daily of progesterone for three days. The bleeding promptly subsided. A short mild period followed the completion of the progesterone therapy. The biopsy again showed

hyperplasia. Patient was then instructed to take her basal body temperature daily and to report to the clinic the third week of each cycle. During the next three months there was no indication of ovulation by the twenty-third day of the cycle, so a course of progesterone was administered from the twenty-third to the twenty-sixth day of the cycle. By the fourth month spontaneous ovulation occurred and menstruation was normal.

Failure of progesterone withdrawal to result in normal flow suggests the presence of an organic lesion. Another history of interest is that of Mrs. E.D., age fifty, who had bled irregularly and at times excessively for more than a year. Curettage done one year before showed no irregularity of the cavity and the tissue obtained showed hyperplasia. Several months of amenorrhea followed the curettage and then the abnormal bleeding began again. Patient received sublingual progesterone 60 mg. daily until 200 mg. had been given. After three days the patient had good withdrawal bleeding, but the flow continued. A hysterogram was ordered but cancelled because of heavy bleeding. Patient was admitted to the hospital for repeated dilatation and curettage. Curettage again failed to reveal any abnormality of this normal sized uterus. In view of the patient's age, a hysterectomy was performed and a pedunculated fibroid arising from the summit of the endometrial cavity was found. This patient had both functional and organic bleeding. The organic lesion was missed even on repeat curettage. A hysterectomy was performed because of the failure of the hyperplasia to respond to adequate progesterone therapy. This patient had functional and organic bleeding.

Summary in Brief

1. The patient with menstrual irregularity can best be cured by effecting ovulation.

2. Metabolic problems should be corrected.

3. Progesterone or estrogen-progesterone substitution therapy can be well employed.

4. Hormone therapy is not indicated in a normal ovarian cycle (look for obscure organic lesions).

THE USE OF PSYCHOTHERAPY FOR SERIOUSLY DISTURBED PATIENTS*

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In previous communications having to do with the concept of the treatment of mental illness within a hospital environment which is planned as a cultural pattern of therapeutic significance by Wall, Hamilton and others,[1-3] the various component parts of such a treatment program have been described. A further review of the extensive literature having to do with the scope and methods of psychotherapy[4-6] is indicative of the many ways in which various therapists have attempted to influence the course of emotional illness in their patients. In the present study, reference will be made to the application of some of the principles of psychotherapy, the validity of which has come to be understood by clinical research and practice as they are employed in the setting of a modern psychiatric hospital, that of the New York Hospital, Westchester Division.

In recent years it has been possible to begin an overall evaluation of our experiences in the development of psychotherapeutic techniques with some degree of perspective together with an increasing objectivity frequently not possible during the course and enthusiasm of developing insight, self-expression and initial accomplishments untempered by accurate self-criticism and comparative study. Various writers[7-9] have helped in this way by tracing and examining the historical growth of our understanding of the human individual in relation to his environment and changing cultural patterns and of his basic personality qualities with which he makes or fails to make an adequate adjustment to the society in which he lives. Such studies indicate that, while much has been gained in identifying rational methods of treatment, the need continues for further research and experience in application.

The urgency for new definitions of individual and social goals being

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forced upon society by growth and development in the physical sciences[10] is being felt by scholars and laymen alike as atomic and other scientific research outstrips social improvement and offers the choice of unlimited destruction[11, 12] or more complete understanding in the matter of human endeavor. The practice of psychiatry and of psychotherapy is today inextricably a part of this problem and an active role is being taken by them in the direction of attaining a concept of health and philosophy that will reflect our best ability to understand ourselves and others, or as Hocking[13] has phrased it, of "What man can make of man." Maturity of the human personality must be gauged in the final analysis not solely in terms of freedom from crippling anxiety and fear but by the achievement of a sense of personal and social values which is compatible with the basic biologic characteristics of the individual.

Sir Russell Brain[14] in giving the recent Annual Oration for the Medical Society of London chose as his subject: "The Need for a Philosophy of Medicine," and he said, "we speak of medicine as both a science and an art, and surely these two aspects are complementary. Science is analytic, explaining or seeking to explain, the whole in terms of the part; art is intuitive, and sees in the whole something more than can be explained as the sum of its parts." In considering that "medicine alone takes as its province the whole man," he reminds us that this has been the traditional quality of medicine, and we realize that it should continue to be the basis upon which medicine should relate itself to the individual patient and to society. The methods by which the therapist through his personality applies the theories and products of scientific research constitutes the art of medicine and as such becomes the definitive, motivating force of psychotherapy.

In looking back briefly over the past an appraisal of some of the more significant steps in the understanding of the psychotherapeutic process will make more tangible the objectives of therapy in relation to the causes and nature of symptoms as we have come to recognize and interpret them. Throughout history man has been preoccupied with trying to understand himself in relation to the universe and the infinite, while at the same time he has been engaged in the struggle to survive in the physical sense against many threatening forces. Failing in the latter aspiration, much of his life experience has been concerned with his efforts to substitute an idealistic immortality for a physical one, and the intelligence which distinguishes him primarily from the other mammals has

enabled him to accumulate a store of knowledge with which he has been able to discriminate between fact and fancy. He has also by this means been able to modify and control his environment to his advantage, and his ability to communicate through language has obligated him to a type of responsibility in social living not shared by any other species. Attempts to solve the riddle of death and of beginning life as related to the function of the instinct for survival constitute the earliest concepts of magic and religion, and no prehistoric culture has been discovered that does not give evidence of protective measures finding expression in religious rituals, totems and taboos.[15, 16] Eventually the conflicts arising from the need for instinctual satisfactions and the relationships of pain and pleasure[17] as basic mechanisms in an increasingly complicated social order gave rise to conditioned patterns of behavior often at variance with the established order of living. This in turn led to his experiencing the effects of fearfulness which he was either not able or not permitted to recognize as such or to express in direct or effective ways. Anxieties thus engendered became the source of feeling, thinking and behavior which we identify as symptoms of mental illness. To be no longer an animal unable to speculate as to his future but rather to have become the twentieth century civilized man that we credit ourselves with being today has meant the slow traversing of many stages and types of cultural experimentation in which the human personality has many times been victimized by its failures. In spite of this, however, man has demonstrated a continued resilient adaptive capacity to gain understanding and insight from which one can justifiably derive a sense of reassurance and optimism.

From a clinical psychiatric standpoint the beginning of a scientific formulation of the application of psychotherapeutic principles began some years after the first experiments with hypnotism when, during the American Civil War period (1860-70), the English physician, James Braid, and the French practitioner, A. A. Liebeault, began to test in an objectively unbiased way the observed effects of psychological reactions on the physical organism. Zilboorg[18] thus states in his historical review that "the birth of psychotherapy through Braid and Liebeault was a unique event in medical history." With the subsequent quickening of the psychological pulse through the research of Freud and the psychoanalytic technique, the significance of cause and effect became more apparent and accessible to analysis, though not without much heated

controversy, and there followed a phenomenally rapid increase in the usefulness of psychotherapy during the past forty years of medical progress. The roster of therapists who have pioneered in seeking methods of applying dynamic insight in the treatment of patients continues to grow[5, 7, 18, 19] and from such efforts psychotherapy is becoming more specific in the practical sense and more capable of being tailored to suit the patient's individual needs.[11, 20-28]

In the present study a review of some twenty cases was made in which psychotherapeutic techniques were used in relation to other aspects of hospital treatment with emphasis being placed on helping the patient to center his attention on the reality of his situation and of remotivating himself toward dealing with his problems and symptoms in positive, aggressively constructive ways. This is, accordingly, an attempt to communicate individual experience in psychotherapy, which is, of course difficult to express with complete objectivity or with the aid of statistics. In so far as it is possible to judge, improvement seemed to be related to the mechanisms described.

For the patient who can most benefit by hospital care, the combination of good physical care, nursing attention and medical treatment with psychotherapy provides the best opportunity for clinical response. Playing the role of the "good parent" it is necessary to remember that as O'Neil[29] says, "the physical health of an individual is important in itself" and that "physical symptoms or injuries are not always mere expressions of inner conflict." Attitudes of the patient toward actual physical illness which is limiting or painful may then be modified gradually as reaction patterns become known. Eventually, as the patient becomes more responsive and less fearful it is important to help him recall or perhaps realize for the first time the various roles[30] in which the therapist has functioned and to compare them with the ways in which other persons such as physicians, teachers, friends, parents, ministers, employers, and other associates in reality can help him in ways that are unique to their positions. Reorientations of this nature are of value in helping the patient begin to resolve his fears, hostilities, guilt and defensive behavior.

One of the present group of patients expressed great concern and perplexity relative to his previous treatment which had followed formal analytic lines, and he was frightened and resentful that he could still be incapacitated by an impulse to jump to his destruction which he

could scarcely control until his hospital admission. His course in therapy is suggestive of several of the therapeutic methods now being considered.

Mr. L., age thirty-two and single was the second of two sons born to intelligent, well educated parents who, however, were poorly adjusted within themselves and to each other so that the family life was a most disturbed one during his early years. The father, meticulous and overly conscientious, was forced into marriage by the occurrence of a pregnancy. The mother was unable to accept the feminine role in life and tried by all means at her command to discredit men generally and the members of her own family in particular. Assailed by guilt over her conscious rejection of her sons, she would then become oversolicitous of and seductive to them until she would again become absorbed in an extra-marital affair or in her teaching and civic work. Both the patient and his brother felt very much left to their own devices, although they developed a close emotional attachment to one of a series of governesses. It happened, too, that the older brother tried on three separate occasions to destroy the patient before he was five years old; once by releasing his baby carriage, once by pushing him into the water, and once by pushing him out of an upper barn window from which his fall was broken by a pile of manure. During his school years the patient made what appeared to be a reasonably effective social adjustment, and his superior intelligence made scholastic progress relatively easy with special achievements in creative writing. During several years of military service he found himself in conflict in regard to his sexuality because of masturbatory guilt, lack of confidence in his relationships with girls, and some homosexual experimentations. Shortly after his military separation he began to have severe nocturnal anxiety attacks for which he eventually sought psychiatric help, and for two years he received therapy with improvement. However, in attempting to work as a publishing journal editor he became panicky, left his job, and then felt the almost irresistible urge to jump from his eighth-floor window.

During his present hospital period he has been able to verbalize his preoccupations and feelings of depersonalization which had prevented him from participating realistically in his previous treatment, since he could tolerate his association with his physician only as long as he could believe that he was "a third person" looking on without actually becoming involved. He felt that he had been rejected by his parents and that he had been hostile in his reactions to breast-feeding and to toilet train-

ing. Believing also that he had bitterly resented the "punitive, unrewarding attitude" of his elders relating to his early bowel control experience, the act of defecation became to him a "giving of himself" which he eventually associated with doing work of any kind, so that no amount of monetary remuneration was sufficient to justify or reward his best efforts. In addition, it became safe only to be "passive" and he developed the phantasy-conviction that if he "appeased" and appeared to be "dumb and unresponsive," he could not only hope to avoid "destruction" but also, in a measure, gain a defensive upper-hand in his relations with others. Consequently, he devised a world of his own thought in which he remained detached and aloof from others, feeling "secure" in the delusion that he was "omnipotent" and that he could ignore, accept or control the behavior of others at will and indeed, as he said, "destroy them by simply lifting a finger" if he chose. Anxiety and rage reactions developed when he could not actually control his associates nor compete successfully with them, and he took refuge in the mechanism of either sabotaging his own accomplishments or of leaving them unfinished. The world to him became a giant "womb" and he became preoccupied with thoughts of "deep, dark depths of water" which were both fascinating and terrorizing to him. Fearfully competing with his brother during childhood while at the same time admiring him, he felt that his impulse to jump from a high level was a repetition of his desire to "identify with" his brother and he suspected that there "might also be an element of sexual attraction in this reaction."

Admittedly fearful following his admission, he was nevertheless articulate, and in responding to the initial contact with the therapist, it was apparent that he was a sensitive person of refinement and social standing. Physical examination was within normal limits and a beginning rapport was carefully sought by permitting and encouraging him to express his immediate concerns and reactions to having come to the hospital. These had to do with the nature of the hospital program and particularly with the schedule and frequency with which "psychotherapy" interviews would be planned which he expected to be his greatest source of help. This reflected his previous experience in analytic therapy, and he later described his fear of not being "seen frequently enough," since in the beginning, he saw this as his only means of "controlling" the situation and protecting himself from being influenced against his will. He expressed relief, however, at being in the security

of the hospital but he asked for reassurance as to being protected from doing some impulsive harm to himself or others. Following a direct explanation of the nature of the hospital, its facilities and purposes in addition to a brief discussion of what would be expected of him, he became notably more at ease and able to respond to some humorous remarks as a subsequent interview time was planned. The next several interviews were devoted to some discussion of his current reactions but included also a briefly comprehensive survey of his history, personality, interests and general experiences. This information, being elicited in an orderly fashion, included references to all of the phases of his life and served several purposes considered to be therapeutically important at the beginning of treatment. This procedure provides the patient with an orientation of the therapist's scope of interest and creates a beginning frame of reference as to the significance of experience and personal values. An attitude on the part of the therapist that is accepting, and desensitizing without indication of personal intensity of feeling or prejudice at this time has proved to be helpful in minimizing threat when the patient is fearful, while at the same time permitting him the use of whatever defensive measures he may feel necessary at first. Brief, tactful inquiry of this type opens the way for further discussions of conflict material, and indicates a willingness on the part of the therapist to share in a responsible way whatever the patient may consider to be of importance.[22, 23]

Detailed descriptions, or even identification of all the more subtle psychological "give and take" reactions that characterize a beginning patient-therapist relationship are difficult to record but must be deliberate in the mind of the therapist at the time in relation to his interpretation of the patient's need.[31-34] In the case of Mr. L. it developed later that he had been much relieved during the first interview to note that the therapist had managed as he said, "to sense my fear of a close contact while at the same time conveying in a respectful way his acceptance of my hostility and wretchedness."

As contacts continued briefly during the making of rounds, in passing at various activities or at greater length in scheduled interviews, Mr. L. expressed various emotional reactions relating to his experiences or symptoms and he began to use the therapist in various ways. He would attempt to dominate, to tyrannize and to seduce. He asked for direction and would then disobey. Seeking reassurance, comfort and

pampering, he tested the therapist for some indication of falseness, and he displayed the whole gamut of affective display with frequent recourse to well-intellectualized verbalizations. Efforts to invalidate the therapy process were expressed in his comparisons with his previous therapy and he was chagrined to be required to review such comparisons with more and more accuracy until he was surprised at his eventually being able to evaluate the gains that it had provided in a realistic way. Similarly, in all of his reactions he was encouraged and at times authoritatively required to measure his preoccupations and his behavior against his immediate environmental situation until he gradually began to identify a new kind of satisfaction in his experience which, as he said, was unburdened by his former pathologic anxieties in his relationships with people and even with his mother about whom much of his conflict had centered. Carefully timed and formulated discussions with the mother enabled her to participate constructively in the therapy by lessening her need to relate to the patient in unhealthy ways. Attention to small courtesies and considerations of his feelings without oversolicitation were important in convincing him of the consistency of the therapist's attitude, but little or no quarter was given to unreasonable demands or conniving duplicity as these mechanisms were uncovered and evaluated in discussion periods.

Having had little support or direction from his passive, self-centered and hypochondriacal father, he described his reluctance at first in asking for concrete suggestions but when he did, there was a lack of his former veiled defiance and he revealed a childlike naivete that presaged a significant change in his attitude. He said, "I have been discouraged lately at my wanting to be alone in my room to withhold myself from the others in a spirit of retaliation for the inconsiderateness, but at the same time I want to be with them. How can I make myself feel that they like me and that I do not have to be afraid of being hurt?" Emphasis was then placed in a suggestive way on small evidences of his growing ability to respond to reality situations and he was commended on his response to a letter of inquiry for his advice about a literary matter. In this and other ways, as much attention was paid to his over-all behavior as to his specific symptoms. He continued to revert to his need to identify the origins of his symptoms by striving for early recollections, but he began to be less concerned with the accuracy of these researches in comparison with his increasing confidence in relating more successfully with people and

with less anxiety and hostility. Eventually after about five months he began to express "a good feeling" of "being unified" and of being able to accept others without the feeling that they were about to destroy him and of translating his conviction of having omnipotent power into a new idealism having the quality of a faith. This puzzled him, since he had always considered that "God was an all powerful force" which he had identified with other threatening influences whose expectations of him were quite beyond his capacities and whose mercy would be only a temporary respite before his destruction. He described a new feeling of security reflecting an appreciation of the best qualities in others while at the same time a toleration of their hostilities and shortcomings.

This brief review of the general course of therapy for one patient has been condensed to the point of much over-simplification but it serves to illustrate some of the objectives of treatment as they were achieved by the patient-therapist relationship[35, 36] in a carefully planned environment in which the patient gradually achieved a more normal living experience.

In a second instance, Mr. D. was admitted at age forty after having had an acute psychotic break in which he experienced ideas of reference, depression and confusion. Intelligent, an accomplished concert pianist and music teacher, he became convinced that he had broken a law in failing to include the name of his school on a brochure relating to his concert work and he became panicky at having a certain book in his library which he felt was not consistent with the policies of the school in which he taught. Following admission, considerable time was spent in repetitiously orienting him as to the nature of the hospital while his confusion gradually cleared. He was also reassured daily as to his assumption that his entire life and career had been ruined by his illness. As rapport developed through his dependency and his need for reassurance, he became more relaxed in his attitude and gradually he was able to describe his experience. At first notably defensive in avoiding any expression of hostility towards his parents he eventually talked of his life-long conflict about his relations to them and his feelings of rejection by them. It was confirmed by history that they had sent him to his grandmother's for his first eight years and had favored his younger sister. They had also disapproved of his interest in music and even after his admission indicated their belief that his illness justified their attitude and could be used to change his mind about his music.

Here again this patient was able to develop a relationship with the therapist in which he could gradually be motivated and encouraged to participate in reality activities while at the same time reviewing his past adjustments with new understanding. He came to realize that he had been compulsively trying to achieve a successful perfection in his music in the mistaken belief that this would result in the acceptance by his parents that had previously been denied him and at the same time there were indications of his trying to prove himself in the masculine sense. With evidences of a changing attitude on the part of his parents, he was overly anxious to accept their new overtures for help and financial support but he was advised to wait until he had discussed the matter a number of times. Eventually he was able to plan his future with their help but without further feelings of defeated obligation and subjugation. It is thus apparent that in both cases just cited an important element in the psychotherapy was the contact by the therapist with the significant relatives in affording them the opportunity for expression and carefully planned and timed discussions of their relationships with the patients. At the same time, the patient is helped to understand the therapist's purpose in working with the relatives as being valuable in the patient's interest rather than a "taking the family's side" process.

A third case in the present series illustrates the use of similar efforts in the treatment of a severe depressive reaction with underlying long-standing compulsiveness. Mr. D. was a forty year old, competent hair-dresser of good intelligence who had completed only high-school education before it was necessary for him to become self-supporting. Never able to express either recognized or unrecognized hostilities and fears relating to his emotional dependence and his psychosexual development, he became characteristically compulsive to a moderate degree, hypochondriacal, and over a period of years suffered with neurotic fatigue states which he attributed to overwork. Relieved temporarily of a depressive episode by means of electroconvulsive treatments and again by ambulatory insulin and histamine injections when his symptoms recurred, he was admitted in a severely depressed state with a hopeless and suicidal trend. He repeated over and over his belief that he should be "put away" where he would no longer be a problem to his family, and he did not wish to see his wife whom he had not seen for two months while he visited with a sister. He expressed surprise when he was advised to see his wife but he came to realize her proper concern,

her interest, and her need to share his illness. This occurred in spite of his guilt reactions and the unconscious threat which she represented. Visiting periods were carefully planned, and interviews gradually uncovered his feelings of sexual inadequacy, although for a considerable time he would revert to his complaint that he was concerned only about his "head pressure" and his inability to sleep. After several months during which the patient was helped to participate in group activities, given support and encouraged to talk of his earlier experiences, he was able to accept the realities of his living with diminishing anxieties so that his first afternoon away from the hospital with his wife was mutually quite satisfactory. His use of the therapist as a father substitute and his assimilation of educational information, interpretations and guidance reduced his immature dependencies, and without the use of electroconvulsive treatment he was able to leave the hospital in a much improved condition with a favorable prognosis.

In the remaining seventeen cases comprising the group in this study some of the more significant measures that proved to be helpful in stimulating useful responses to reality situations included: firm resistance on the part of the therapist to demoralized denials of reality problems, reassurance as to status, gauging the response to be expected to the adaptive capacity, temporary assumption of discipline and decision-making responsibility, tactful, unthreatening temporizing with seduction and rage behavior, planned or supervised use of visiting periods for relatives, repeated identification of reality circumstances, stimulating new methods of creative expression and experience, identifying the meanings of symbolic patterns of expression and behavior, and detailed attention to the patient's individual dignity as a person.

It has been said that "specific techniques grow out of the uniquely personal way in which an individual therapist relates to his patients,"[37] and many times a therapist in training has to be guided away from his conscious or unconscious attempts to emulate in detail the ways of his preceptor or of some other therapist whose success he admires. The acquisition of knowledge, self-discipline[22] and dynamic insight must be combined with the acceptance by the therapist of his own personality and his use of it in the best interests of the patient. In this way, the more widespread application of carefully planned psychotherapeutic techniques based on the dynamic understanding of personality and psychobiological relationships which we possess today will be increasingly

effective in the amelioration of symptoms and in the promotion of preventive mental hygiene.

In summary, a consideration of several various aspects and methods of psychotherapeutic practice with seriously disturbed patients in relation to dynamically planned hospital care has been presented, emphasizing the goal of helping the patient to meet his reality circumstances to a maximum degree through psychotherapy.

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SECTION ON MICROBIOLOGY*

with the

SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE†

*Abstract of Paper***

Presented at the Meeting, February 17, 1954 at The New York Academy of Medicine

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Program

PROGRESS IN ELECTRON MICROSCOPY OF NORMAL AND PATHOLOGICAL TISSUES

a. *Introduction – Background****

KEITH R. PORTER, Presiding Officer
Rockefeller Institute for Medical Research

b. *The Composition and Fine Structure of the Ground Substance and Fibrillar Components of Connective Tissue*

HENRY BUNTING,†† Yale University School of Medicine, New Haven, Conn.

c. *Some Observations on Virus-Cell Relationships*

COUNCILMAN MORGAN, College of Physicians and Surgeons, Columbia University, N. Y.

d. *Certain Features of the Fine Structure of Normal Tissue Cells****

GEORGE E. PALADE, Rockefeller Institute for Medical Research

e. *Electron Microscopy of Malignant Cells****

KEITH R. PORTER, Rockfeller Institute for Medical Research

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* Gregory Shwartzman, Chairman; Thomas P. Magill, Secretary, Section on Microbiology.
† Frederick A. Mettler, Chairman; Irving Graef, Secretary, Society for Experimental Biology and Medicine.
** Manuscript received July 1954.
*** No Abstract received.
†† Deceased, no Abstract received.

The Appearance of Herpes Simplex, Influenza, Vaccinia and Fowlpox Viruses Within Sectioned Chorioallantoic Membranes Examined in the Electron Microscope[*]

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Examination of ultracentrifuged preparations of infected allantoic and vesicle fluid in the electron microscope has shown particles presumed to be herpes simplex virus.[1-3] Many of the particles were noted to have a central area of depression containing a small body.

Previous study in the electron microscope of sectioned chorioallantoic membranes infected with herpes simplex virus revealed intranuclear particles considered to be virus.[4] Because removal of the methacrylate had produced distortion of fine structure, a study of thinner sections with the embedding substance left in place was undertaken.

Particles 30-40 $m\mu$ in diameter were seen within nuclei believed to be in early stages of infection. These particles apparently increased in size in the nucleus to 100 $m\mu$ with the addition of a single membrane. The membrane was separated from the central body by a clear zone. Following release of the particles into the cytoplasm of the host cell a second membrane developed, increasing the size of the virus to average 130 $m\mu$ in diameter. Thus, within the cytoplasm and in the extracellular space the virus of herpes simplex appeared to be composed of a central, primary body, 30-40 $m\mu$ in diameter, enclosed by a double membrane.

Because ultra-thin sections were found to permit high resolution microscopy, it was felt important to determine whether a virus smaller than herpes simplex also possessed a clearly defined structure. Accordingly, chorioallantoic membranes infected with influenza (PR8) virus were sectioned. On the surface of the entoderm were seen dense, spherical particles, 70-100 $m\mu$ in diameter, which were believed to represent the virus. They were composed of a central body, surrounded by a membrane.

Vaccinia and fowlpox viruses have been shown in ultracentrifuged preparations to possess a limiting membrane and a central area of increased density.[5-7] More recently, in thin sections a nucleus-like structure was seen in vaccinia.[8-9] Such observations have been confirmed. Vaccinia, morphologically similar to fowlpox, possessed a limiting membrane and a finely granular inner structure. At one margin was located a dense, granular, nucleus-like particle separated from the remainder of the virus by a clear zone. After release from the host cell these viruses were seen to possess a double membrane enclosing a dense inner body.

Probable sites of development of fowlpox virus within the cytoplasm of the host cell were shown, but it was emphasized that the data obtained to date were insufficient to define the precise manner by which the virus differentiates.

SUMMARY

The internal structure of four viruses sectioned within infected tissues is described. Both influenza and herpes simplex viruses showed a central body contained within limiting membranes. Fowlpox and vaccinia possessed a fine granular material and a small, eccentrically located zone of

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greater density, resembling the nucleus of a cell.

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THURSDAYS — 9:00 P.M. — 10:00 P.M. Station WNYC-FM — 93.9 megs.

January 6 CURRENT PROBLEMS IN BLOOD TRANSFUSION—Peter Vogel, *Associate Hematologist, Director of the Blood Bank, The Mount Sinai Hospital, New York.*

January 13 THE PITUITARY THYROID RELATIONSHIP IN NORMAL AND DISORDERED THYROID STATES—Sidney C. Werner, *Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York.*

January 20 POLYCYTHEMIA VERA: ITS COURSE AND TREATMENT—Louis R. Wasserman, *Hematologist, The Mount Sinai Hospital, New York.*

January 27 PRINCIPLES IN THE MANAGEMENT OF ANEMIA—Maxwell M. Wintrobe, *Professor and Head, Department of Medicine, University of Utah College of Medicine, Salt Lake City.*

MONTHLY PANEL MEETING ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

Third Meeting — Third Series

1954—1955

Friday, January 7, 1955—4:30 P.M.—Room 20 at the Academy

Subject: **PREVENTIVE USE OF PSYCHOTHERAPY IN CHILDHOOD**

Moderator:

LAWRENCE S. KUBIE — *Clinical Professor of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; Faculty, New York Psychoanalytic Institute*

Panel Members:

CLEMENT B. P. COBB — *Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Assistant Attending Pediatrician, The New York Hospital*

MARIANNE KRIS — *Faculty, New York Psychoanalytic Institute*

MILTON I. LEVINE — *Associate Professor of Pediatrics, Cornell University Medical College; Associate Attending Pediatrician, The New York Hospital*

MARIAN C. PUTNAM — *President, The James Jackson Putnam Children's Center and Director of Child Development, Boston, Massachusetts*

FUTURE MEETINGS

Friday, February 4, 1955

Subject: THE EFFECTS OF TOBACCO SMOKING
Moderator: G. JARVIS COFFIN

Friday, March 4, 1955

Subject: PARKINSON'S DISEASE: MEDICAL AND SURGICAL MANAGEMENT
Moderator: SAMUEL BROCK

Friday, April 1, 1955

Subject: MANAGEMENT OF PANCREATITIS — ACUTE AND CHRONIC
Moderator: CHARLES F. WILKINSON, JR.

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PROGRAM — January 26, 1955 — 8:00 P.M. — Room 440

1. CIRRHOSIS OF THE LIVER WITH PORTAL HYPERTENSION IN CYSTIC FIBROSIS OF THE PANCREAS — Paul A. di Sant' Agnese — Department of Pediatrics, The Presbyterian Hospital, New York

2. THORAZINE/RAUWOLFIA SERPENTINA COMBINATION IN THE TREATMENT OF ESSENTIAL HYPERTENSION (PRELIMINARY REPORT) — Harold B. Eiber — The Medical Service of The New York Medical College, Flower and Fifth Avenue Hospitals, New York

3. THYROIDAL UPTAKE AND PLASMA LEVEL OF RADIOACTIVE IODINE IN THE DIAGNOSIS OF UNTREATED HYPERTHYROIDISM — Robert A. Newburger, Solomon Silver, Stephen B. Yohalem and Sergei Feitelberg — The Mount Sinai Hospital, New York

4. OCCURRENCE OF MYELOID LEUKEMIA IN PATIENTS WITH METASTATIC THYROID CARCINOMA FOLLOWING PROLONGED MASSIVE RADIOIODINE THERAPY — S. M. Seidlin, Edward Siegel, S. Melamed and A. A. Yalow — Medical Division, Montefiore Hospital, New York

5. THE SIGNIFICANCE OF THE DEPRESSION OF INDIVIDUAL COMPLEMENT COMPONENTS FOR THE DIFFERENTIAL DIAGNOSIS OF RENAL DISEASES — Kurt Lange, Eugene J. Wenk and Lawrence B. Slobody — New York Medical College, New York

6. CLINICAL EXPERIENCE WITH THE INJECTION OF STREPTOKINASE INTRAMUSCULARLY IN THE TREATMENT OF INFECTIONS AND EDEMA Joseph M. Miller, John A. Surmonte, Milton Ginsberg—Veterans Administration Hospital, Fort Howard, Maryland—and Frank A. Ablondi, A.B.—Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

7. DEBRIDEMENT OF BURN SLOUGH BY PEPTIDASES RECOVERED FROM CLOSTRIDIUM HISTOLYTICUM — Edward L. Howes, Ines Mandl, Ph.D. and John D. MacLennan — Department of Surgery, The Presbyterian Hospital, New York

8. CLINICAL EVALUATION OF THE TOBACCO BALLISTOCARDIOGRAM — Leon Pordy — The Mount Sinai Hospital, New York

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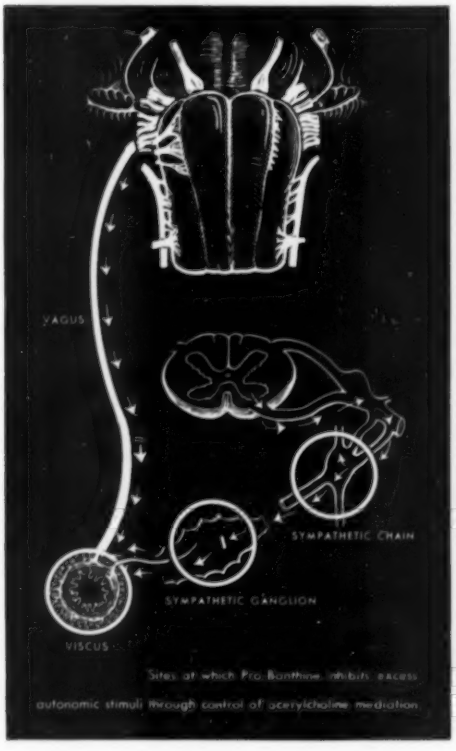

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1. Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

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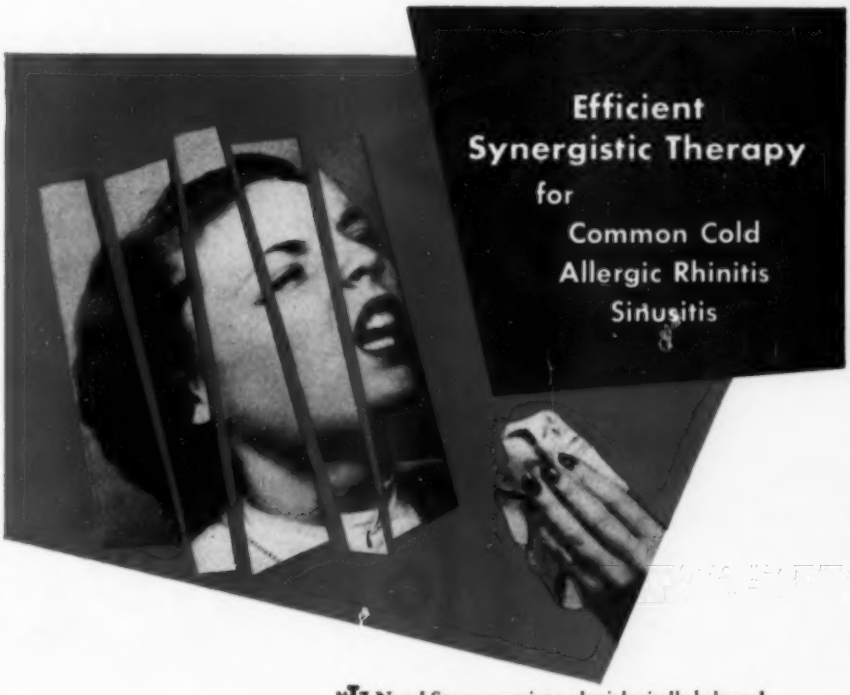

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1. Malleson, J.: Lancet 2:158 (July 25) 1953. 2. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc. 1953, p. 23.

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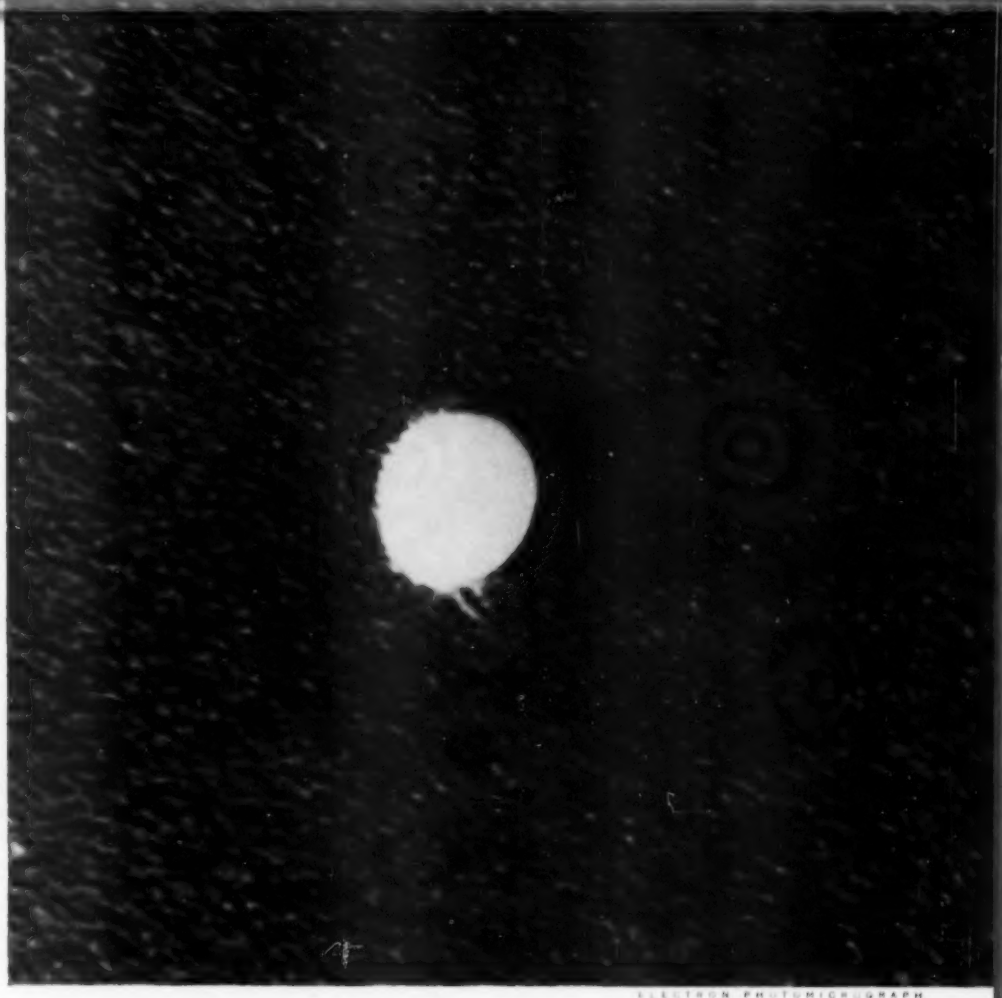

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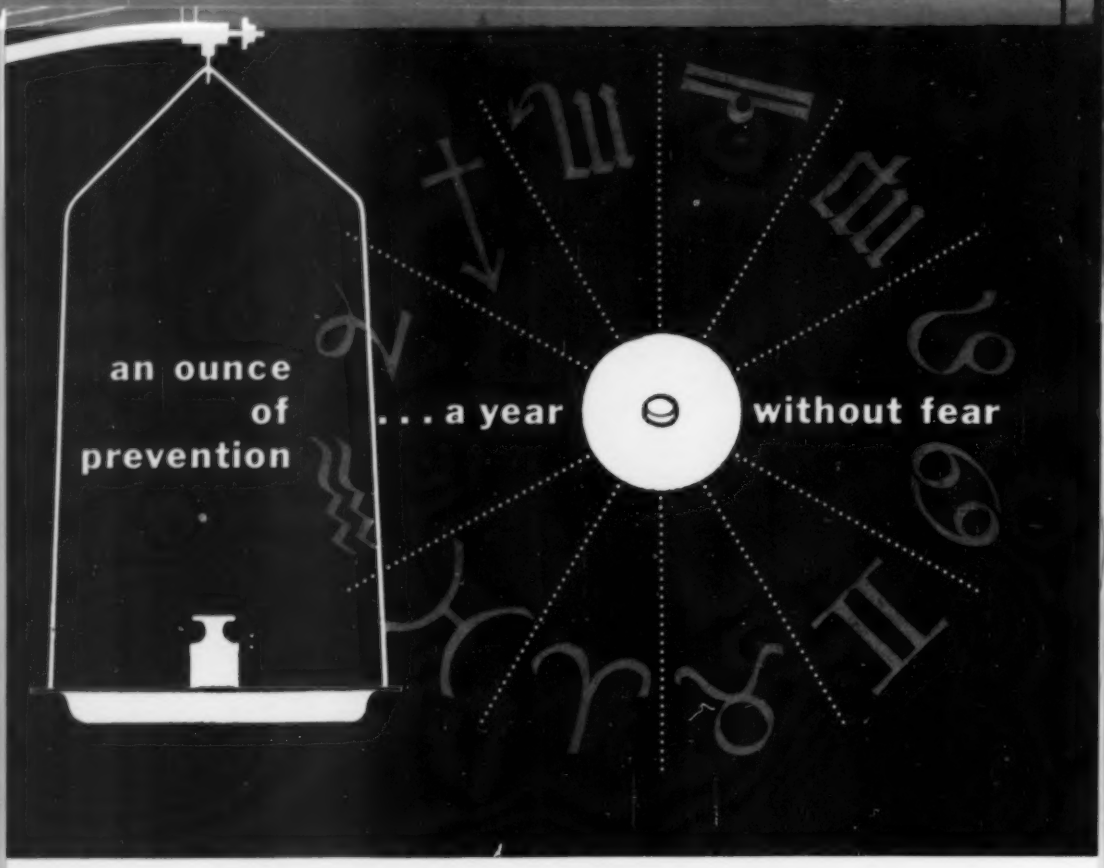

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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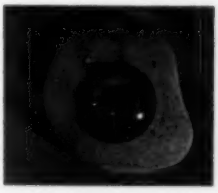

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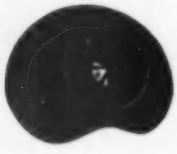

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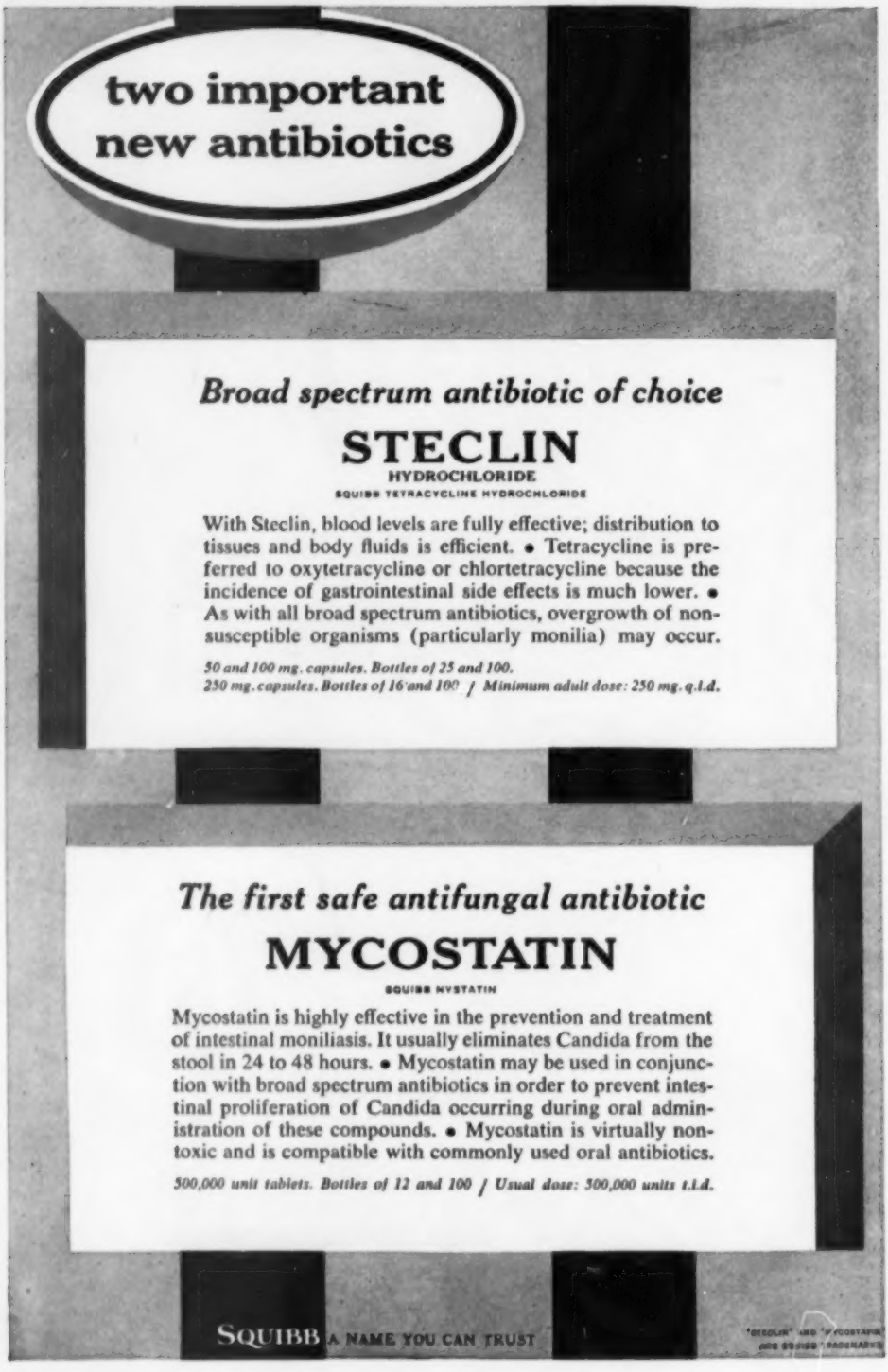
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